This Page Is Inserted by IFW Operations and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.

S/N: 09/872,086 CHIR-15900/00US



- PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

C12N 15/86 21) International Application Number: T/C	A1	(43) International Publication Date: 27 May 1999 (27.05.99
21) International Application Number: T/C		
22) International Filing Date: 13 November 1998 30) Priority Data: 60/065,793 14 November 1997 (14.11 71) Applicant (for all designated States except US): CON LABORATORIES LIMITED [CA/CA]; 1755 S enue West, North York, Ontario M2R 3T4 (CA) 72) Inventor; and 75) Inventor/Applicant (for US only): PARRINGT [CA/CA]; 45 Main Street, Bradford, Ontario L3Z 74) Agent: STEWART, Michael; 6th floor, 330 Universit Toronto, Ontario M5G 1R7 (CA).	.97) U NNAUGH Steeles A'). ON, Mai 124 (CA	BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW MX, NO, NZ, PL, PT, RO, RU, SD, SB, SG, SI, SK, SL TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPC patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasiar patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europear patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of
		t least one optimal heterologous splice site is introduced to the alphavirus be Semliki Forest virus following administration of the vector to a host.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

NL.	Albania	28	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Pinland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
ΑZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistun
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	77	Trinidad and Tobego
BJ	Benin	IE	fretand	MIN	Mongolia	UA	Ukraine
BR	Brazil	ĬL	krael	MIR	Mauritania	UG	Uganda
BY	Belarus	IS	liceland	MW	Malawi	US	United States of America
CA	Canada	П	Raly	MX	Mexico	UZ	Uzbekistan
CIF .	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CC	Congo	KB	Kenya	NL	Netherlanda	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
a	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cube	KZ	Kazakatan	RO	Romania		
cz	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	u	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SR	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF INVENTION ALPHAVIRUS VECTORS

FIELD OF INVENTION

5

The present invention relates to the field of DNA vaccines and is particularly concerned with modified alpha virus vectors for use in such vaccines.

BACKGROUND OF THE INVENTION

10 Semliki Forest virus (SFV) is a member of the Alphavirus genus in the Togaviridae family. virus particle contains a single copy of a ssRNA genome with a positive polarity that is 5'-capped and 3'polyadenylated. It functions as an mRNA and naked RNA 15 can start an infection when introduced into cells. infection/transfection, the 5' two-thirds of the genome is translated into a polyprotein that is processed into the four nonstructural proteins (nsPl to 4) by self cleavage. Once the ns proteins have been synthesized 20 they are responsible for replicating the plus-strand (42S) genome into full-length minus strands (ref. 14). These minus-strands then serve as templates for the synthesis of new plus-strand (42S) genomes and the 26S subgenomic mRNA (ref. 1 - Throughout this application, various references are cited in parentheses to describe more fully the state of the art to which this invention Full bibliographic information for each citation is found at the end of the specification. disclosures of these references are hereby incorporated 30 by reference into the present disclosure). This subgenomic mRNA, which is colinear with the last onethird of the genome, encodes the SFV structural

proteins. In 1991 Liljestrom and Garoff (ref. 2) designed a series of expression vectors based on the SFV CDNA replicon. These vectors had the virus structural protein genes deleted to make the way for heterologous inserts, but preserved the nonstructural coding region for production of the nsPl to 4 replicase complex. Short 5' and 3' sequence elements required for RNA replication were also preserved. A polylinker site was inserted downstream from the 26S promoter followed by translation stop sites in all three frames. An SpeI site was inserted just after the 3' end of the SFV CDNA for linearization of the plasmid for use in vitro transcription reactions.

10

15

20

25

30

Injection of SFV RNA encoding a heterologous protein have been shown to result in the expression of the foreign protein and the induction of antibody in a number of studies (refs. 3,4). The use of SFV RNA inoculation to express foreign proteins for the purpose of immunization would have several of the advantages associated with plasmid DNA immunization. For example, SFV RNA encoding a viral antigen may be introduced in the presence of antibody to that virus without a loss in potency due to neutralization by antibodies to the Also, because the protein is expressed in vivo the protein should have the same conformation as the protein expressed by the virus itself. concerns about conformational changes which could occur during protein purification leading to a immunogenicity, protective epitopes and possibly immunopotentiation, could be avoided by plasmid DNA immunization.

3

In WO95/27044, the disclosure of which is incorporated herein by reference, there is described the use of alphavirus cDNA vectors based on cDNA complementary to the alphavirus RNA sequence. Once transcribed from the cDNA under transceptional control of a heterologous promoter, the alphavirus RNA is able to self-replicate by means of its own replicase and thereby amplify the copy number of the transcribed recombinant RNA molecules.

SUMMARY OF THE INVENTION

10

15

20

25

The present invention is concerned with modifications to the alphavirus cDNA vectors described in the aforementioned WO 95/27044 to permit enhanced replication of the alphavirus. In the present invention, a heterologous splice site is introduced into the alphavirus replicon sequence, particularly that of Semliki Forest virus (SFV).

Accordingly, in one aspect, the present invention provides an expression vector comprising a DNA molecule complementary to at least part of an alphavirus RNA genome, which DNA molecule comprises the complement of the complete alphavirus RNA genome regions which are essential for replication of the said alphavirus RNA, and further comprises a heterologous DNA sequence capable of expression in a suitable host, such as a human or animal host, said heterologous DNA sequence being inserted into a region of the DNA molecule which is non-essential to replication thereof, and the DNA molecule being placed under transcriptional control of a promoter sequence functional in said animal or human host, wherein at least one heterologous splice site is

4

provided in the DNA molecule to prevent aberrant RNA splicing of the alphavirus.

The alphavirus molecule is a large molecule and, accordingly, there is a high probability of cryptic splice sites, thereby impairing the replication of the alphavirus and hence its ability to express heterlogous DNA is impaired. By introducing the at optimal heterologous least one splice accordance with the present invention into alphavious replicon sequence, any splicing is likely to be directed at the heterologous splice site rather than any cryptic splice sites, restores the function of the SFV replicon when removed, and may improve transport of RNA from the nucleus (ref. 6).

10

In the constructs provided herein, the promoter is placed upstream of the 5'-end of the alphavirus sequence, such that the resultant transcript has an authentic 5'-end, which is required for the efficient replication of the alphavirus RNA replicon.

In addition, there may be provided at the 3'end of the Semliki Forest virus segment, a hepatitis delta virus ribozyme sequence to ensure proper in vivo cleavage at the 3'-end of the sequence. Any other convenient sequence may be employed to achieve this effect.

The heterologous splice site sequence may be provided by the nucleotide sequence of the rabbit β -globin intron II, as described in reference 5. Such heterologous splice site sequence may be inserted into the complement sequence at any convenient location which generates perfect splice junctions. This

precludes replication of the alphavirus, unless it is authentically removed by splicing..

I have identified five suitable sites in the SFV replicon, which are contained within an EcoRV-SpeI fragment of the replicon which is 8010 bp in length (Fig. 3). The first such site is a Ppu-MI site, at position 2719 within the EcoRV-SpeI fragment.

5

10

15

20

In constructing the modified vectors provided herein, the EcoRV-SpeI fragment is cut with Ppu-MI at position 2719 and made blunt-ended with Mung Bean nuclease, which removes three bases from the SFV sequence. A blunt-ended β -globin II intron, which is 536 bp long, is ligated into the site and replaces the missing three bases with sequence added to the 3'-end of the β -globin intron sequence (Fig. 1).

The other four suitable sites for insertion of the Intron are the PvuII sites at bp 2518, 3113, 6498 and 6872 of the EcoRV-SpeI fragment. Insertion of the Intron is achieved by cutting with PvuII (a blunt end cutter) and the blunt-ended β -globin II intron sequence (Fig. 2) is ligated into one or more of these sites.

In a further aspect of the present invention, there is provided a cloning vector suitable for expression in a host cell of an heterologous DNA sequence, which comprises a DNA molecule complementing to at least part of an alphavirus RNA genome, which DNA molecule comprises the complement of the complete alphavirus RNA genome regions and has a cloning site for insertion therein of a heterologous DNA sequence capable of expression in a host cell, said cloning site being located in a region of the DNA molecule which is

6

non-essential replication to thereof; a promoter sequence functional in said host cell and transcriptionally controlling said DNA molecule, said promoter sequence being placed upstream of the 5'-end of the DNA molecule such that the resultant transcript. had an authentic 5' end; at least one heterologous splice set provided in the complement of the DNA molecule to generate perfect splice junctions in the alphavirus in order to prevent aberrant splicing and an additional DNA sequence at the 3'-end of the DNA molecule to direct proper in vivo cleavage at the 3'end of the reactant mRNA transcript.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows the DNA sequence of the β -globin intron II including three additional nucleotides at the 3'-end thereof (SEQ ID No:1);

Figure 2 shows the DNA sequence of the $\beta\text{-globin}$ intron II (SEQ ID No:2);

Figures 3A to 3C show the DNA sequence of the 20 EcoRV-SpeI fragment of Semliki Forest virus replicon (SEQ ID No:3);

Figures 4A to 4D show the DNA sequence of the pSFV link (SEQ ID no: 4) prepared as illustrated in Figure 5;

25 Figure 5 shows construction of pSFVlink (11060 bp) from pSFVl using a linker sequence (SEQ ID nos: 5,6);

Figures 6A to 6D show the nucleotide sequence of plasmid pMP76 (SEQ ID no: 11, prepared as illustrated in Figures 8A to 8D;

Figure 7 illustrates subsections of plasmid pSFV link (see Figure 5);

7

Figure 8A to 8D show the construction of plasmid pMP76 from plasmids pMP53, pMP70, pMP47, pMP55 and pMP71;

Figures 9A to 9B show the construction of plasmids pMP53, pMP54 and pMP55 from plasmid pMP52;

Figure 10 shows the construction of plasmid MP52 from pUC19 using a linker sequence (SEQ ID no: 7,8);

Figures 11A to 11B show the construction of plasmids pMP46, pMP47 and pMP70 from pUC19 and fragment from pSFV link, prepared as seen in Figure 7; and

Figures 12A to 12B show the construction of plasmid pMP71 from plasmid pCMV3.

GENERAL DESCRIPTION OF INVENTION

As discussed above, the present invention provides a modified alphavirus DNA. The alphavirus preferably is Semliki Forest virus. In particular, the present invention provides a cloning vector for heterologous gene expression in a host, such as an animal or human.

20

25

30

The promoter sequence may comprise a promoter of eukaryotic or prokaryotic origin. Suitable promoters are the cytomegalovirus immediate early promoter (pCMV), although other promoters, such as the Rous sarcoma virus long-terminal repeat promoter (pRSV), since, in the case of these and similar promoters, transcription is performed by the DNA-dependent RNA polymerase of the host cell. Additionally, the SP6, T3 or T7 promoters can be used, provided that the cell has first been transformed with genes encoding SP6, T3 or T7 RNA polymerase molecules which are either inserted into the chromosome or remain episomal. Expression of

8

these (SP6, T3, T7) RNA polymerase-encoding genes is dependent on the host cell DNA-dependent RNA polymerase.

The heterologous DNA insert may comprise the coding sequence for a desired product, which may be a biologically active protein or polypeptide, for example, the heterologous DNA insert may code for HIV sequences, e.g., an immunogenic or antigenic protein or polypeptide, or a therapeutically active protein or polypeptide. The heterologous DNA may also comprise additional sequences, such as a sequence complementary to an RNA sequence which is a self-cleaving ribozyme sequence.

10

15

The DNA vectors provided herein may be administered to a host, including a human host, for in vivo expression of the heterologous DNA sequence, in accordance with a further aspect of the invention, in order to generate an immune response in the host, which may be a protective immune response. The DNA vectors may be further formulated into immunogenic compositions for such administration.

BIOLOGICAL DEPOSITS

Certain vectors that contain the Semliki Forest
virus replicon and referred to herein have been deposited with the American Type Culture Collection (ATCC) located at 10801 University Boulevard, Manassas,
VA 20110-2209, U.S.A., pursuant to the Budapest Treaty and prior to the filing of this application.

30 Samples of the deposited plasmids will become available to the public upon grant of a patent based

q

upon this United States patent application and all restrictions on access to the deposits will be removed at that time. Non-viable deposits will be replaced. The invention described and claimed herein is not to be limited in scope by plasmids deposited, since the deposited embodiment is intended only as an illustration of the invention.

Deposit Summary

Plasmid ATCC Designation Date Deposited

10 pMP76

EXAMPLES

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific Examples. These Examples are described solely for purposes of illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitations.

Methods of molecular genetics, protein biochemistry and immunology used but not explicitly described in this disclosure and these Examples are amply reported in the scientific literature and are well within the ability of those skilled in the art.

20

EXAMPLE 1

5

15

.20

25

This Example describes the construction of plasmid pMP76 as outlined in Figures 5, 7, 8A, 8B, 8C, 8D, 9A, 9B, 10, 11A, 11B, 12A and 12B.

Plasmid pSFV link was created by restricting plasmid pSFV1 (Gibco) with BamHI. This plasmid was then ligated with a linker (SEQ ID no: 5 and 6) to produce plasmid pSFV link (Figures 4A to 4D, Figure 5).

Some of the SFV replicon fragments were subcloned by restricting pSFVlink with EcoRV and SpeI and 10 isolating the 890bp EcoRV-SpeI fragment. This fragment was then restricted with EcoRI and the 1906bp EcoRV-EcoRI, the 1578bp and 3627bp EcoRI-EcoRI and the 899bp EcoRI-SpeI fragments isolated (Fig.7).

The 1909bp EcoRV-EcoRI SFV fragment was cloned into EcoRV-EcoRI restricted plasmid pMP52 to produce plasmid pMP53 (Fig.9A). The 899bp EcoRI-SpeI SFV fragment was cloned into EcoRI-SpeI restricted pMP52 to produce pMP54 (Fig.9A). Plasmid pMP54 was then restricted with SpeI and made blunt-ended with Mung Bean nuclease. The plasmid was then restricted with BglII, dephosphorylated and ligated to the hepatitis delta virus ribozyme linker (SEQ ID nos. 9 and 10), that had been phosphorylated, to produce pMP55 (Fig. 9B).

Plasmid pMP52 was created by ligating a linker (SEQ ID nos:7,8), into the EcoRI site of pUC19 (Fig.10).

The 1578bp EcoRI-SFV fragment ws cloned into 30 the EcoRI site of pUC19, to produce pMP46 (Fig.11A). This plasmid was then restricted with PpuMl and made

11

blunt-ended with Mung Bean nuclease. The rabbit ß-globin intron II PCR fragment (Fig.1) was made blunt-ended with Mung Bean nuclease, phosphorylated and ligated to the PpuMI restricted pMP46 to produce plasmid pMP70 (Fig.11B).

The 3627bp EcoRI SFV fragment was cloned into the EcoRI site of pUC19 to produce pMP47 (Fig.11A).

Plasmid pCMV3, which contains the CMV promoter, Intron A sequence, BGH poly A sequence and SU40 poly A sequence, was restricted with NdeI and EcoRV. The 3191bp NdeI-EcoRV fragment was isolated and dephosphorylated. The 1321bp NdeI-EcoRV fragment was isolated and restricted with SacI. The NdeI-SacI fragment of 334bp was isolated (Fig.12A). The isolated SacI-EcoRV PCR fragment containing the 5'-end of SFV was ligated to the previously isolated 334bp NdeI-SacI fragment and the 3191bp NdeI-EcoRV fragment to produce pMP71 (Fig.12A and 12B).

10

15

Plasmid pMP53 was then restricted with EcoRI
and BamHI and ligated to the isolated and
dephosphorylated 2151bp EcoRI fragment from pMP70
(Fig.8A). This ligation was then restricted with EcoRV
and the 4057bp EcoRV-EcoRI fragment purified(Fig.8A).

Plasmid pMP47 was restricted with EcoRI and
the 3627bp EcoRI fragment isolated and dephosphorylated
(Fig.8B). Plasmid pMP55 was then restricted with
BglII, dephosphorylated and restricted with EcoRI. The
985bp EcoRI-BglII fragment was isolated and ligated to
the previously isolated EcoRI fragment from pMP47
(Fig.8B). The ligation reaction was then

12

phosphorylated and the 4612bp EcoRI-BglII fragment isolated.

Plasmid pMP71 was restricted with EcoRV and BamHI then dephosphorylated. This fragment was used in a 3-way ligation with the previously isolated 4612bp EcoRI-BglII fragment from pMP47 and pMP55, and the 4057bp EcoRV-EcoRI fragment from pMP53 and pMP70, to produce pMP76 (Figs.8B and 8C).

The 5' end of the SFV replicon was produced by PCR

amplification of pSFV1 using primers SFV-5'-3 having
the sequence

5'-TCCACCTCCAAGGATATCCAAGATGAGTGTG-3' (SEQ ID no: 9 and SEQ ID no: 10 respectively) between the CMV promoter and the 5' end of the SFV replicon. The resulting PCR fragment was restricted with SacI and EcoRV (Fig. 13; SEQ ID no: 11) and the fragment isolated.

15

SUMMARY OF DISCLOSURE

In summary of this disclosure, the present invention provides a modified alphavirus-based expression vector wherein at least one optimal splice site is introduced to the alphavirus replicon to prevent aberrant splicing of the alphavirus genome; and improve transport of RNA out of the nucleus.

Modifications are possible within the scope of the invention.

WO 99/25859

REFERENCES

Fulginiti, V.A., Eller, J.J., Sieber, O.F.,
 Joyner, J.W., Minamitani, M. and Meiklejohn, G.,
 (1969) Am. J. Epidemiol. 89 (4), 435-448.

5

- Chin, J., Magoffin, R.L., Shearer, L.A., Schieble,
 J.H. and Lennette, E.H. (1969) Am. J. Epidemiol.
 89 (4), 449-463.
- 10 3. Jensen, K.E., Peeler, B.E. and Dulworth, W.G.
 (1962) J. Immunol. 89, 216-226.
 - Murphy, B.R., Prince, G.A., Collins, P.L., Van
 Wyke-Coelingh, K., Olmstead, R.A., Spriggs, M.K.,
- 15 Parrott, R.H., Kim, H.-Y., Brandt, C.D. and Chanock, R.N. (1988) Vir. Res. 11, 1-15.
- 5. Chapman, B.S.; Thayer, R.M.; Vincent, K.A. and Haigwood, N.L., Nucl. Acids. Res. 1991, 19: 3979-20 3986.
 - 6. Huang, Zhi-ming and Yen, T. S. Benedict, Molecular and Cell Biology, July 1995, p.3864-3869.

14 CLAIMS

- 1. An expression vector, comprising a DNA molecule complementary to at least part of an alphavirus RNA
- 5 genome, which DNA molecule comprises the complement of the complete alphavirus RNA genome regions which are essential for replication of the said alphavirus RNA and further comprises a heterologous DNA seuence capable of expression in a host, said heterologous DNA
- sequence being inserted into a region of the DNA molecule which is non-essential to replication thereof, and the DNA molecule being placed under transcriptional control of a promoter sequence functional in said host, wherein at least one heterologous splice site is
- 15 provided in the DNA molecule to prevent aberrant RNA splicing of the alphavirus.
 - 2. The vector of claim 1 wherein said promoter is placed upstream of the 5'-end of the DNA molecule such that the resultant transcript has an authentic 5'-end.
- 20 3. The vector of claim 2 wherein said promoter is the cytomegalovirus immediate early promoter.
 - 4. The vector of claim 1 which further comprises an additional DNA sequence at the 3'-end of the DNA molecule to direct proper in vivo cleavage at the 3'-
- 25 end of the DNA molecule.
 - 5. The vector of claim 4 wherein said additional DNA sequence comprises a hepatitis delta ribozyme sequence.
 - 6. The vector of claim 1 wherein the heterologous splice site sequence is provided by the DNA sequence of the rabbit ß-globin intron II.
 - 7. The vector of claim 6 wherein the heterologous splice site sequence is inserted into the DNA molecule

15

at a location which generates perfect splice junctions and restores the function of the SFV replicon when removed.

- 8. The vector of claim 1 wherein the alphavirus is a Simliki Forest virus.
- 9. A cloning vector suitable for expression in a host cell of an heterologous DNA sequence, which comprises:

a DNA molecule complementing to at least part of an alphavirus RNA genome, which DNA molecule comprises the complement of the complete alphavirus RNA genome regions and has a cloning site for insertion therein of a heterologous DNA sequence capable of expression in a host cell, said cloning site being located in a region of the DNA molecule which is non-essential to replication thereof;

a promoter sequence functional in said host cell and transcriptionally controlling said DNA molecule, said promoter sequence being placed upstream of the 5'end of the DNA molecule such that the resultant transcript had an authentic 5' end;

at least one heterologous splice set provided in the complement of the DNA molecule to permit aberrant RNA splicing of one to generate perfect splice junctions in the alphavirus; and

20

- 25 an additional DNA sequence at the 3'-end of the DNA molecule to direct proper in vivo cleavage at the 3'-end of the reactant RNA molecule.
- 10. The cloning vector of claim 9 wherein said heterologous splice set is provided by the DNA sequence 30 of the rabbit ß-globin intron II.

WO 99/25859

16

- 11. The cloning vector of claim 9 wherein said additional sequence comprises a hepatitis delta ribozyme sequence.
- 12. The cloning vector of claim 8 wherein the alphavirus is a Semliki Forest virus.
 - 13. The cloning vector of claim 8 which has the identifying characteristics of plasmid pMP76 shown in Figure 8D.
- 14. The cloning vector of claim 8 having SEQ ID no:
- 10 11.

SFV bases <u>-</u> ٣ the with the \(\beta\)-globin intron II Nucleotide Sequence of

799 450 450 360 480 540 240 300 180 atggttacaa tttgtaacga tggaaatatt ccctctgct gtatcaccat attgtctcct atcacttttt aacaattgtt catgttatat ttagcttgca actttctcta agttttagag ctggctggcg cttctcttt gatgtccctt gttgacaacc ccaaaccggg ttgtaaaatt atcatcctgc tactctgagt acttcagcac catataaatt ttttcgcta agaatgggaa tcgttaaact gattgtaagt ttctactct caggtc aatatttctg gaggataaaa ttatttgtca catcctggtc ctttttccta ttgttctttc ggtgttgtt tttctttcac tgtaactttt attatattgt gaaacaacta atgccttctt tttcattttc atcagggtat gataaggtag gataattttg tcacttttgt tgtttgagat ggacccttga aagttttcag tgatatacac aaccatgttc gtgagtttgg ggaggggca ggaccctcat cttattttct atttttaaat tttcaaggca ataattaaat cttattggta

Nucleotide Sequence of the β -globin intron II

420 240 300 360 120 180 480 atggttacaa tttgtaacga atcacttttt aacaattgtt tggaaatatt ccctctgct gtatcaccat attgtctcct catgttatat actttctcta ttagcttgca ctggctggcg ctttctcttt gttgacaacc agttttagag ccaaaccggg ttgtaaaatt gatgtccctt atcatcctgc tactctgagt ttttcgcta agaatgggaa tcgttaaact gattgtaagt acttcagcac catataaatt tttctactct gaggataaaa ttatttgtca ttgttctttc tgtaactttt attatattgt aatatttctg catcctggtc ctttttccta ggtgttgtt tttctttcac tttcattttc atcagggtat gaaacaacta tgtttgagat ggacccttga aagttttcag gataattttg tcacttttgt gataaggtag atgccttctt tgatatacac aaccatgttc ggaggggca ggaccctcat cttattttct atttttaaat tttcaaggca ataattaaat cttattggta gtgagtttgg

2/39

FIG.3A Eco RV-SpeI Fragment of Semliki Forest virus replicon

120000	42244225	π	trtacdcaca	aataccacto	tataccc	.09
gcagr	geeerea	ayaa cyac	100000000000000000000000000000000000000	to constant		C
atgcgcagcg	gaaga		aragerae	aaayaaace	gragegge	V (
gggaag		agagatcgca	aa	ccgacctgca	ccgtcat	180
ctacqcca	gctgaat	ctacctt	tgcctgcata	gacgtcac	gtgtcgtacg	4
cadccdaa	ggcc	ccaggacgtg	ctgta	Ŭ	ctgta	_
atcaggcg	gaaag	ac	tattggattg	ggtttgacac	caccccgttt	_
att	gctagca	cgcgtatcca	Ü	aaactggg	acgagca	^.
tgttacag	caggaaca	gactgt	cagca	actgag	agactcgg	~~
aaactgtcca	U	gaagcaattg	aaccttgc	cacagtc	ttctcggt	_
gatctac	gtaca	gaaa	tactgag	tggcact	ccctccgt	_
cacct	aaggtaaaca	tectttae	gtaggt	tacc	tcatgtga	0
ggtacgta	ಹ	Ď	cggcctg	cggt	gggta	
ccataac	cacgcgg	gattcct	tgcaa	\mathbf{o}	gtcaaag	30
aaaqaqtc	ttccct	atgcacctac	gtcccctcaa	tctgt	caaatgac	TT.
catacta	gaccgac	cacaccggag	gacgcacaga	ttag	aa	
agaggata	tgtgaac	gaaca	aaacac	acacgatgaa	gaactatctg	w
ttccdatt	geegteg	atttagcaag	tgggcgaggg	aatacaaggc	agaccttgat	02
atgaaaa	tctgggt	ag	acttac	ctgct	tg	1080
aaacgagg	atgcac	catgtacaag	aC	cccagacaat	aaggt	14
cttcag	ttaactcgtt	cgtcatcccg	agcctatggt	gcc	cgcaatccca	20
tcagatca		gcttttggcc	aagaagacca		aatacctgtt	26
tcg	cgtcagccag	ggatgctgaa		aggagaggtt	ď	32
gactaga	agcc	accctcgtc	cccatcgcgc	cãoa	gggagtcgtc	38
categ	ttgaagaact	agagtatcac	tgca	ggtcgtg	aacacctcgc	44
gagaattg	ί	acagccgaac	gacgtactac	taggaaatta	cgtagttctg	50

390822 4 2380 4 2380 3000 3060 2820 2880 2940 2160 2340 2400 2520 2580 2640 2700 2760 2100 2460 1920 2040 1980 1620 1680 1740 1800 1860 agcatttaag gtactatgga cctcacccgc ccctgcgtcg ggccacattg ggctgcgcct gcctgtcctg cgagaacaac cggattcttc atgtcataaa gcactacgga cacaggacag aaagcagctg aacgctggcc tctggtcacc ccgcgggaag tgccgtggac cctaattgct cgcctacgaa ctttggggtt atatgacggc tttgagcgag ccatattgcc agctgaaaga agaggaagcg agcagagcag ccataattac ccttgtatgc tggtgtggaa gtaactttac ttgaaggacc aaagcctggt tttgcaccaa ccctgtatta gaggctgggc catctcaggg tcatagacac ctctgctggc tgtctacgtt ggtgtcgtcg ccaagcaatg gcactgaagt ggaaactata tccatgaatt ccaaacacga tgaagaagca tgcacctct agtttcaagc agaaagtcag gcgtcaagag tagtaggagt aggtcgacgg tgttgggcga aatgaaaatc gaggataggc attccacagg atgaaggtga gagtggagca ttgaatgaaa ccgaaggtgt acatgcttcc acagcagcag cacaacatct acggccatcg aaacccataa ctgctaaacg cattccggta tgcggagacc aagactacag agcctcgtga gttaacgacg ttggcccccg ccggtccctg ttcgtcaaca gagaactacg aaaaatgct aacccccgt ggcggttacc cgacaaaata gttttctgcc gcgtccagtc catcgtgtta cgaagtcatg gcagaaggtg gacgcgcact cctatcaaac agcgaacgtg gacagcagag agtggtggcc gaacttcaac cccgtgcaac tgactccatc ttcgcttgc agtggtgtta ccaggaaata cgggaggcc cgacgtagat agagctaacc ggcaccatat tattattaag gagctccaag cgaaagggag caccgacgag atcggccatt gcacgaccaa ggattaaggt aagaagaaca tccagaacaa gaatcagatt cttactctcc acagtggcct tggacgaggc ctcggagcaa agcttaaggt gacgttgcac agccaggaga accgtggaca acgccgtaag atgtactgct gcaagtctgc tgttggtggg tcaggccgtc aggagaactg gggaaaacag tggtgtacaa cgtcgctgaa agtacgtgtt ccgtgctcaa taacacataa taccatgtgg ttgacctgg gagcacgtga gaagaatggc gtggacgcgt gacactgccg gaggacagag agtatatcca ggcaagatgc accaagccca cagttggact aaaggggtat ggcgatccct aatatgatgc agcggcaaga gggacaagta atcctatatg cttgttaaac gggctgaaga ccgggatcag gtgaaaataa agggtcctac agegeeacta gttcacggac actgacgccg tegggtttgg tccccgcaga

5/39 4620 3840 3720 3780 4560 3240 3,600 3660 3900 3960 4020 4080 4140 4200 4260 320 4380 4440 4500 3420 3480 3540 3180 3300 3360 3120 caaccaggct tccggtgaac cccgctgctg ccatctattc tgatgacgtg tcgtaagggc aaacgaacag caaccgcagg gttctccaac gagtgccgtg taagagagca tggaactgta gggagcagca ccacgctgta cgctgtctac aagttgggag cgcaatgaca gaacattcac agcttacgga ctcgtctgca ggcagttatc tgagtggctg gtgctacgac gctgcagatg agctgccagg ggctttgcct gcgaattggc aatccctcaa gcagagacaa agttgctcaa gcctggtggg tgcaagaggc gatccaaatg tgtgccgcta gcgtagccat gtacgaaatt ctaacgcccg cagcctttaa accccgtcat taattcctat acgccatgaa tcttgatgag gcagaaagtt tgttcttgct ataccaagct cctacagagt atgccgcaac cgggcaagca gcagtagggt agtacaacct tggtctttgt gcgccgatag tggcccagac gacaacatca gaaggggacc tcactgagca aggctgcagc accatctact acggctgtgg ccggacagca tactttgaag gtgccctgcc aaatggccgt tgcggctcgt caccagatga gttaacgcag ctggacaatg aatacagaag tgtgcaccat tatggattca cagtggcata aggttcgact tgtgtcgacc cccggcggca tcctccttaa acggttaaag ctggtgagtg aatgtcacag tgacatgagg actgacgttg cgctgacgtg gagagtgcac cgaaacaatg tcccaggaca aacagtcatg aaacagactg cggaagagat gctgtactcg tgtcaccagc cacggccggg agcggctgtg gactgaagcg gctttctgtg tgacgccggc actgctaaaa agccgttgtt ctctacgcta cgtggcgaag tgagtacaag ccacgtcctg ctaccagcag tggaaggatg cctgaagggg gtcaccgctg gcacaattaa aggaagccat tggcagagat aagccatgca cgtgcacaga tatgcagggc tctctgccac ccgccgaagt cgttcagcgg acgccacgga cagacttggt ctgacgggtc acgcgctggg catcaacacc aaatcagcga gcccggattg gaaagagacc aaatccaacc gactgccggc gaatccacca atgcgctacg acagacctgg gacatacctt taagagggta ccctggtggc tcacttggtt aagaaatcc gagctgacca gctattgata gcgcctaatt cgggcagtgg tccacaggag acagcaatgg tacagtacca atatgcctat gattccgatt agagtgttgc gacatagcca ggggatggcg acaccagtgg tacgccgata tttgacaacg tatgccggag ctggaagcta gcagaaagaa ctgccgcacg gtcaataaag cgacgcaggg ctaagtttag acggaattca cttgggggag cactgggata

5400 5700 5340 5640 5940 0909 6180 4920 4980 5040 5100 5160 5220 5280 5460 5520 5580 5760 5820 5880 0009 4740 4800 4860 ggaaagaccc ccccgtgtac gtgcaacgaa atacgacgca gagaaactgc cgtggagtgc acctatccgg agctgctgcc cagattcacg ccagtctcgc cagattgtac ctgcccggcg cagtgccgtc ctcggacact cgcacaactg ggagaagctg ctcgtcttcc ctcgatctac gaacccgatt gctgcctttg tactttcgga gaaggttctc atctacgacg aggcatcgcg gcgaccggtg ttgctcatct ttcccatgga gagcgacatt ccgccaccaa caqtqttcaa atgctaaaca aaggcccgaa aacacaga catcgggggc caatcgcagc taacagatga agagtcgata ggtaccccg cgactgtacg atattttctc atctccagtg atactgagag gtgacatcga tggacctcga gcgcggcgga ttaggaacaa cctccgggat taaagtgcga ggaccaccga ctgaacccgc gcatggtggt agtatgccgc gtgctagcgg atggactcgg accaaattga gaggctaata gacaggctca tacgcggttc cccgatgtag tcgtaccaga tgcttggaca taccaccagc tgggaagaat ctgcaggagg ccagggacga aggcagcaca ccaaaattgg gatgcgttgg gaggtgat agtccgcgga gacttggact ttgcagtcgt gacgtacacc gcagaccatg cttgcctccc aggactgcgt caagttaaaa gtgcagaagg actacagaac cggagaatat sacctatgtg cttggttccg cataccaaca attctcaagc aacagtggcg gtcggatagt acatcatgcg actacccacc caaagtcact aaaatccgtt aatgtacccg agctgcatac gcctgcccca gcacgaggtc actaggccgc gcacccatcg cacggtggtg agtgacggct ccctgaaccc taggtcacac tgtagatggg ttcagtggtt acgagggttt gctacccagt gaattacco tggttgacgg gctacccgaa atgcctgctc agaacatcac agacccacaa aacgagatgt atttacaaca aggaggagaa aaatgcagat acatgaaagc acgtaggccg tgatcgaaag ttcagaacac aaatgcgaga cagatgtgca gcccgaagag gaaagccgac actttgacga acgtcctgcg tegecegeet cgaaatacca cgacggtacc atcggtcgtt ataccatgtc ctcccatagt tacttggaca ccgtcaccct aacgtcacgc ttcaagcgct ataaccactg ttgttcgcta gtcgacatga ggcagcggac gatgcggtcc tractgctga aaagtggaga acgggagcgg tcccctaccg tacctatcca aagctccggt gcagaacgga cctccaccgc ccggcgccga acgttcggcg gacttcgacg ttcccctcc ctgttcgacc gaccactcag gagccaatgg gacctggcgg actgccagcg

6/39

FIG.3E

7/39 7020 0969 7080 7140 7200 7260 7380 7440 6840 0069 1320 7500 7560 7620 7680 7740 6720 6780 6540 0099 0999 6300 6360 6420 6480 cgcactatta cggtggctcc taaatgcgct agaagaagac agcagcaaaa aaagaatgtg gtagtgtttc ctgggggcct cgcagataag gttagggtaa agccatggcc acacctctac tttacggccg cccacttaag agacaggcga gtcgtgggtc ttttgtggg cgaactggag attgtttgat agacccggtt tcttacaggt cgaggcagcc cggagctatg caccatagca cggcgacgac cggcatccac aacagaaaa ggaaaaacgc ccacagtaac ctcgggtggt cattgggctc gtgtttcaga agcaggacga gcttgggggc gtatcctcat gacctgttat tggatcatag acgcaaacgt caggccactc atcagcgccg aaaccaaaga ggaaaaagag acgtgcacac actccttggc agaggtgcgc aacccccata tccacccagg tggacttgat gcttcaagtt ttttgaacat cggccttcat cttacctgtg gaagatcaac gcagcaactc gaagaaaccc gaaaattgaa gaattctgat taggcctccc atgcggctag tgcagaaaat tggtcacttg ctgatggcgg atgggcgaaa accgcctgcc gctgaagaca ttccggacag ggctgcaaaa aaattgagag ttacatccct ttggccgttg cagtacctgc actggcacgc attaacactg tccgcctgtg ttacgcccta agccaggacg ttggcgaccg gcctctcact ctatcatggg gtgctggttg gatatagcaa cggcccgtcc ttgctcctgc cgcagcccaa acaagaagaa gtatcttcgt ttaatacaca attaattgaa cccagcagat ctccgacaag tgacgctgtc cgtcacacag gccgctaaca tagcaagtgg tgaggtagag ggcgtttaag cgcgatcatc aggggtggat gactttgttt actcactgac agcggagcca aaatgctgtg tcacctacca attcgacaaa gggcaccgca cgctatcctg cagaacgcaa aagccgaaaa aagcaagccg gaaaatgact gggacattaa atcccgggta ccdcdcccdd gacttccagg catctaggta gattggtgcg taattcaagc taaggagact aagactttga acattgcatc tcgaagatct tatccagctg gcatgtttct tggagcagag acggagtgat tgaagatcat tttttgacag agttgggtaa gtgacgaggt caatggcat ccggtggcgc gacaatgaga gaagaaagac catgaagatt cagacatgtc tegeaategg ttagggtagg ggcggtccta cgtcgtccc aaccaaacca gtggcactaa taggatccag ttaatgatcc tttggggaaa atgaaatcgg agcagggtac aacatcgttc aacatggagg ggattcatag cgcctgttca cgagcactga accttggcga aaagtccagg agggaattag atgtcggccg ctagagacgg

FIG.3F

rcaatdgcat	ataaccataa	ctgtataact		cgcaacaaga	cctgcgcaat	2
accc	gtccgcctca	cggaaactcg	gggcaactca	tattgacaca	ttaattggca	9
taattoga	cttacat	ttaattcg	acgaataatt	ggatttttat	tttattttgc	Ō
ttaatt	aati	aaaaaaa	aaaaaaaa	aaaaaaaaa	aaaaaaaaa	7.980
	רכו					8010

FIG.4/

Nucleotide sequence of pSFVlink

1020 1080 1140 1200 1260 099 720 780 840 900 096 540 009 180 240 480 120 300 tccctgtat accgacgtca gtgaacggaa ctgggtgtcc ctccgcaaga tacactgaga ggtaaacaat aagaaaatca cacgcggagg atgcacacca aactcgttcg attgaggctg gagtcattgc accaaattga ccttccagga ctggatagag gctgaatctc gccgtatacc aaaggtgtca ctagcaggcg aggaacatag gaagaccccg tgccacctcc gccgtcgca gttacaggcc atctacattg ccacctgaaa gtacgtagtt cgtgacgtat aagagtctca catactagcg gaggatagtt tccgattgtg aacgaggaag ttcagagttt tcaggcgatg gtttgacgcg actgtccatt tgaaaaacct tacgccagac agccgaagtg ttccagctcc gcatgttgat cggcagtgcg gcgcagcgca cgggaaggtg gttcgaggtg gcacctggct tcaaaggaga aaatgactgg accttgatga gggcatttaa tgaaggtgcc cctccgtatt tagggtacgc gattgaatca ccgtcatggc gtcgtacggc cgctgtacca gactcggcaa tctcggtagg catgtgaagg actatctqct catttccgtc cagcggcctc ccccgtttat acgagcaggt ccgccaaagt gagcattttc tcttggatat tatgccctat aaagattttg tggcacttac atctgtgatc acgatgaaga tacaaggcag tgctgcttgt acagtcatgt accatcgtat ggtaaaacgg acagacactg ttgttagtgg cagacaatag cccacgatgg gacacactca taccactgcg aagaaactgg gacctgcaga gacgtcacgt gcaccaacat tttgacacca aactgggccg actgagggaa cacgacgcca ttgcagaagg gcaaatgcca aaacactaac acttacttgc accagacacc accttgcgac actgaggagc taggtgcgat cggcctgtac gtgcaagacc ccctcaacc ggcgagggaa gtgtgacata agattaacca ttggattggg ctacgccaca agcatccttg cgcacagaag catcaagtct aaatgaccat gactgacaaa tacgcacaaa tagctacgca aaaaatcacc cctgcataca tgctgtacat caccggagga gagagaggtc gaacggcgta agcaattgaa cctttacctg ctatgtgccc gcacctacgt gaacacagcg ttagcaagtg gaatgatgtc cgtatccaac gactgtgtgc gcagaaagct gattcctagt gtacaagaa gatggcggat gctacgcgag acagcccatt aggtcacacc tcgagcagga aaaggctcga agatcgcagg ctaccttttg aggacgtgta

9/39

FIG.4E

tcatcccgag	tatg	cctc	aatccca	agatcacg	ttaagat	1500
tttggccaa	gaagaccaag	cgagagttaa	tgttc	ď	gccagg	9
gctgaac	aggagaa	gagaggttgg	gccg	aga	gccttaccac	$\tilde{2}$
ctc	tegegee	gcggagacgg	gagtcgtcga	cgtcgacgtt	gaagaactag	8
tatcacg	tgcagg		accto	cgcgttgaaa	gtcaccgcac	74
gccgaacga	actact	ggaaattacg	tagttctgtc	ga	gtgctcaaga	80
tccaagt	gccccgt	caccctctag	cagagcaggt	aa	acacataacg	36
gagggccg	tta	cgacgga	atgacggcag	tcctac	atgtgga	2
ggccattc	gtccctga	ttcaag	gagcga		tgtacaac	8
aagggagt	caacag	aaactatacc	atattgccgt	cac	tcgctgaaca)4
acgagg	aactacga	aaagtcagag	ctgaaagaac	gccga	acgtgttc	001
cgtagata	atg	aga	aggaagcgtc	gtttgg	tggga	97
gcta	ccccgtt	atgaa	ctacga	ctgaagat	gccgtc	220
aC	actac	gagtc	tggggttc	ggatca	ctgct	8
aga	ũ	aaacacgatc	tggtcaccag	gcaa	gagaactgcc	34
ggaaat	aacg	agaa	cgggaagg	acaagtag	aaaacagt	40
actccatcct	ă	gtcgtcg	cgtggac	ctatatgt	ggct	46
cgct	tccggtac	ctgctggccc	ttgctc	g	gaġcaaa	52
ggtgttat	gag	caatgc	att	atgatgca		28
U	caacatctgc	ctgaag	gtcataaaag	tatatccaga	cgttgcacgc	9
tccagtcac	ccatcg		ctacggag	caagatgcgc	acgaccaacc	2
tgc	cccataat	atagacacca	caggacagac		ccaggagaca	2
Ö	atgcttccga		agcagctgca	gttggactac	cgtggacacg	8
cat	gcagca	ctcag	accc	ggtata	aagg	8
gaaggtgaa	tgaaaatccc	ttgtatgccc	gtcgg	gtg	gtactgctga	94
cgcac	ggataggctg	gtgtggaaaa	tggcc	cgatccctgg	attaaggtcc	0

-1G.40

3840 4140 4320 4380 4500 4560 4080 4200 4260 4440 3240 3660 3900 4020 3360 3480 3540 3600 3960 3180 3300 3420 gccatgcaca cgcacagaag acaattaaaa tctgccacga gccgaagtaa ttcagcggcg gccacggacg gaagccattg tgcagggccg atcagcgaag ccggattgtg aagagacct gcgctacgac agacctggtg cataccttcc atccaaccgc ctggtggctg agagggtacc acttggttgt ctgccggctg atccaccact atcagattga agtggcctgt gaagaacacg tactctccag cagaacaaag gcctaatttc ggcagtggcc agcaacggac gaaaatccag ggatggcgta accagtgggc cacaggagtg Egacaacgga cgccggagaa acgcagggtc aagtttagga ggaattcaga tgggggagat cgccgataaa agtgttgcgc catagccacg ggaagctaga gccgcacgcc caataaagta ctgggataac agaaagaaaa ggacagagct tgacctggac agaatggcaa ggacgcgttc cactgccgga gagcagcaac cactgctgtc atctattcac gttgggagaa gtgccgtgta agagagcaga acgetgtage ctgtctaccg ctttgcctcg gaactgtagg cgtctgcaag agtggctggt gctacgacct acattcacac tgcagatgct cttacggata tctccaactt cagttatcgc accgcaggct catttaagga agaacaacca ctgccaggct ccacattgga ctgcgcctgt ctgtcctgga actatggagt gtagccatcc tccctcaacc agagacaaaa ttcttgctgt aacgcccgtg cccgtcatcc gaattggccg accaagctga tacagagtta gcctttaagg tacaacctgg gccgataggt gtctttgtga gccatgaagc ttgatgagag agaaagttct ggcaagcagg attcctatca agtagggttg tgcaccaagt ctgtattacg gccgcaacag aactttacgg gaaggaccgg agcctggtgc ataattacag cggctcgtac agggaccgc actgagcagc gctgcagcaa catctactgc tgcaccatcc aacgcagct atggccgtca cggcggcatc ccagatgaat gaaggtgtcc ggacaatgta ggttaaaggc ggtgagtgag tgtcacaggc tacagaagtg tccacagggt gaaggtgatt gtggagcacc gaatgaaátt tggattcaat gtggcatacg gttcgacttg tgtcgaccac ctccttaagc ttgggcgaaa acagactgtc Lggcgaagaa cagtcatgtg ctgaagcgga gaagagatag ctgacgtgac tgctaaaacc ccgttgtttc ctacgctaca cggccgggtg cggctgtggt caccagcaa tgaaggggca agtacaagac acgtcctgct caccgctgaa acgccggcag accagcagtg cagcagagga ttctgccc gaaggatgta tttctgtgct tatcaaacat acaaaataat cgaacgtgtg tggtggcctt

5280 5340 5340 5340 5220 5400 5460 5520 5580 5640 5700 5760 5820 5880 5940 0009 0909 4980 4920 5040 5100 5160 4680 4740 4800 4860 ttacaacaaa atgaaagcca tttgacgagc gtcctgcgac gaggagaaaa atgcagatgc gtaggccgca aattacccaa ccgaagagag aagccgacgc gttgacgggt tacccgaaac cagaacacac cggtcgttac cccatagtag gacttggtga gacgggtcgc gcagagatac gcgctgggcg tcaacacctc gcccgcctta aaataccatg acggtacctt accatgtcgc gatgtgcacc atcgaaaga cttcgacgac cctatccaga gctccggtgc gccaatggct tccaccgcgc ggcgccgaga gttcggcgac cagcggacat tgcggtccag gctgctgaaa agtggagaac gggagcggac ccctaccgtg cttggacatg gtcaccctt cctggcggca atgcctatac agaacggatc tgccagcgat gctgaccaca tattgatatg ttccgattca tcccctcccg gttcgacccg ccactcagat cagtaccact cacaactgga cttcggaga gattgtacac ccgtgtactc gcaacgaata acgacgcata gcccggcgaa gtgccgtccc acccgattcc gaccggtgcc tgcctttgac cggacactgg agaagctgtt agtetegeaa cggtgaacga caatgacagc ctacgacgga cgtcttccac cgatctacga gcatcgcgga atgacgtgga gtaagggcta gctcatctt aggttctcct accaggctgc acgaacagat actgagaggg agtcgatacc trgggggcca tacccccgcc atcgcagcgt acagatgaat gcgacattct actgtacgca tccgggatta atttctcct ctccagtgcg gcggcggagc aggaacaagc gacctcgaga ttgctcaatg ctggtgggtc acgaaattca caagaggcaa tccaaatgtc tgccgctacg atggtggttt aagtgcgaga tatgccgcat accaccgact gacatcgact gaacccgcag cttggacaga caggctcaca cgcggttcgg cgatgtagca gtaccagata ccaccagccg gggtgcatat gcagcacaat aaaattggat ggctaataag agaccatgtg gactgcgttt tgcgttggcc ggacagcagc gcccagactg caacatcaga gccctgcctg agttaaaagc gcagaaggta tccgcggaag cttggactgg gcagtcgtgt cgtacacct tgcctcccgc ggctgtggag ctttgaaggt taccaacata tctcaagccc cagtggcgtc tcatgcgta ctgaacccgc acgaggtcga taggccgcgc tgtacccgcc acccatcgga cggtggtgga cggatagttg gagggtttga tgacggctga ctgccccaag aatccgttag acatgaggac tgacgttgtg aaacaatgga ggtcacacca tagatggggt tacccagttt ctgcatacct gagtgcacc tgtactcgta ccaggacagt cagtggttag

=1G.4E

										1	3/	39													
∞	6240	30	36	12	#8	54	50	99	72	780	840	006	960	0	80	14	20	26	32	38	44	50	w	62	Ф
atgcgagaac	ctcc	aacatcacta	acccacaact	cgagatgtca	attcaagcag	aggagactaa	actttgac	attgcatcat	gaagatctag	cca	atgtttctga	gcagag	agt	ď	tttgacagcg	ttgggtaagc	gacgaggtta	tctaggtatg	gacattaagg	ttggtgcgtt	cccgggtaat	gcgcccggcg	cttccaggcc	gaacgcaatt	gccgaaaacg
cgtcacgcaa	caagcgctat	aaccactgag	gttcgctaag	cgacatgaaa	agtccaggta	ggaattagta	gtcggccgaa	gagacgga	atgatcct	tggggaaata	aatcggg	agggtac	cgttca	atggagg	catagt	cctgttcaag	ag	gcac	gcgag	cggtcctaga	ggatccagat	gt	tcgtccccga	caatgagaca	ccaaaccaaa
gaaactgcaa	g	atccgga	ctgctgcctt	gattcacggt	aaagacccaa	atccaca	gtttgata		ttacaggttt	gcagcct	ctat	catagcaa	cgacg	tg	ttgtg	cacttaagcg	aggcgac	aactggaggt	Ď	ctac	cactattata	tacggccgcc	gtggctcccg	aatgcgctga	aagaagacaa
gccaccaaga	tgttcaac	gctaaacaac	ggcccgaaag	cccatggaca	cacacagagg	tacctgtgcg	tgcacaca	cacccaggag	tccttggctc	gacttgatcg	tcaagttc	gaacatc	ccttcatc	Ü	ccccatat	gtttcagacc		adadacc	cata	cctgttatac	gatcatagcg	gcaaacgttt	ggccactccg	cagcgccgta	accaaagaag
cta	ctcg	ggaagaatat	aaa	gcaggaggtt	agggacgaaa		Cg	Ü	ccaggacgac	tacctg	ggcacgcg	ctg	gcctgtgc	tg	g	gcc	aa	cggacagg	T	agag	ctgatt	acatccctac	ccgttgc	agcaactcat	ggcctcccaa
tacagaacgt	cccacca	Ø	ď	gttccgc	Ü	gagccat	atgctgtgtt	atcatcg	caaa	ggtggatc	ctaccaa	gttta	gact	aca	cgctgtca	g	ctaacag	aagtggt	ggtag	taaga	acacag	aat	gcccgtcctt	agcagatg	gctcctgcta

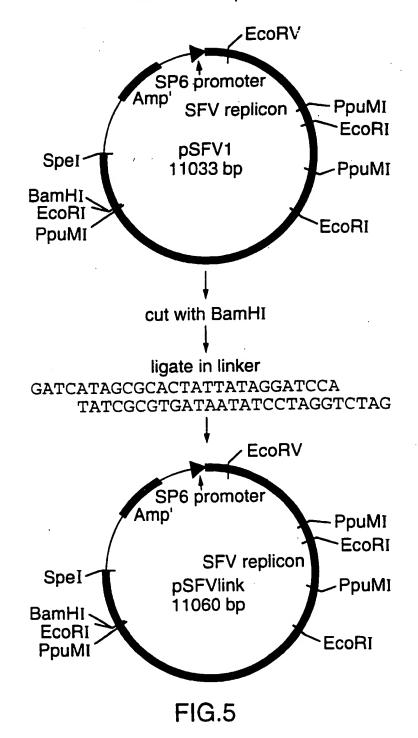
14/39 8400 8460 8460 9000 9240 8340 8520 8640 8700 8760 8820 8160 8220 8280 8580 8880 8940 0906 9120 8040 8100 7860 7920 7980 7800 cactggcagc agttcttgaa ctctgctgaa ccaccgctgg gatctcaaga gacgctcaag ctggaagctc cetteetece cggtgtaggt gctgcgcctt cacqttaagg attaaaaatg atatttccaa gtttgcgtat ggctgcggcg gggataacgc aggccgcgtt ttacataagc aaaaaaaa ctatcctggt atggcattga aaccataact ccgcctcacg gcaagccgac aaatgactgt gcaccgcact cagcccgacc gacttatcgc ggtgctacag ggcaaacaaa agaaaaag aacgaaaact atccttttaa tatctcagtt ggtatctgcg aaccgtaaaa cacaaaaatc gcgtttcccc tacctgtccg teggtegtte agaaagacaa tgaagattga agggtaggca aatggcatat aattggaagc ttggttttta aaaaaaaa gggagaggcg acagaatcag gacatgtcgg gcaatcggcg gcccgtggt acccccgtt ggtaagacac gtatgtaggc ctcttgatcc gattacgcgc cgctcagtgg gcgctgtagg gacagtattt cttcacctag gcttaccgga gggggccttc tagggtaagc tgcgcaattg ctcgctgcgc acggttatcc tgacgagcat aagataccag cagcaaaaga agaatgtgca agtgtttcca cagataagtt aattggcaat tattttgcaa aaaaaaaa ccaacgcgcg aaaggccagg gcaagcagca cggggtctga ctcaatgctc gtgtgcacga agtccaaccc gagttggtag caaaaaggat Lacgaaaaaa caggactata cgaccctgcc gcagagcgag acactagaag aatgaatcgg cgctcactga aggcggtaat aaggccagca cagaaaagt caacaagacc ttgacacatt atttttattt aaaaaaaaa aaaacgcag aaaagagaa acagtaacgt cgggtggtct ttgggctccg aacaggatta aactacggct ttcggaaaaa tttttgtt atcttttcta atgagattat ttccataggc cgaaacccga tctcctgttc gtggcgcttt aagctgggct tatcgtcttg aaaaaaaa agtctgcatt teegetteet gctcactcaa atgtgagcaa gcggctagcc gtcacttgca gcaactcata cagaaaatct aaattgaaaa gaataattgg agatcaacgg agaaacccgg taacaaagcg atccggtaac gccagttacc tagcggtggt agatcctttg attttggtc tgggcgctct agcggtatca aggaaagaac gctggcgttt tcagaggtgg cctcgtgcgc ttcgggaagc cgttcgctcc agccactggt gtggtggcct cagcccaaga gtataacttg aaaaaaaa aaaaaact aagaagaaga tatagcaaga gaaactcggg ttaattcgac atcttcgtat atcatgggtg gctggttgtg

									15	/39)	•												
36	12	100	54	90	99	72	78	840	006	096	0020	008	014	020	026	032	038	044	020	950	062	068	074	10800
gcctgac	ctgcaa	ccagccg	tattaatt	tgttgcca	ctccggtt	tagctcct	gttatgg	gactggtg	ttgcccgg	cattggaa	ttcgatgt	ttctgggt	gaaatgtt	ttgtctca	cgcacat	acctata	gtgaaaacct	cgggagca	taactatg	atgcgactcc	cgcaaggaat	caccataccc	cggt	cacgatgcgt
catccata	ctggcccc	caataaac	ccatccag	tgcgcaac	cttcattc	aaaaagcg	tatcactc	gcttttct	gagttgc	aagtgctc	tgagatcc	tcaccago	gggcgaca	atcagggt	taggggtt	tcatgaca	gtgatgac	aagcggat	ggggctgg	ctctccct	caccgcc	gggcctg	atcttccc	tgatgccggc
ctatttcg	ggcttacc	gatttatc	ttatccgc	gttaatag	tttggtat	atgttgtg	gccgcagt	tccgtaa	gĞ	agaactt	ttaccgc	tctttta	aagggaa	tgaagca	taaaca	tat	gcgttt	gcttctgt	ggcgggtg	atatcg	gccgt	ccccd	ggcga	gtggcgccgg
		accggct	gtcctgcaac	tagttcg	acgctcgt	atccċ	taagt	tgc	agaatagt	gccacata	ctcaagga	atcttcag	tgccgca	tcaatat	tattta	cgtcta	ctttcgt	tca	agcgggtg	gagagtg	actaggtt	cccaacag	agcccgaa	aaccgcacct
cacctatc	agataact	acccacgc	gcagaagt	ctagagta	tcgtggtg	gcgagtt	cgttgtc	tctct	gtcatt	ataatacc	ggcgaaaa	cacccaac	gaaggcaa	tcttcctt	atttgaa	tgccacct	tcacgagg	ccg	dddcdcd	gattgta	cagccca	gagatgg	gcgctca	aggcgccagc
cagtga	ت	ataccgcg	agggccga	tgccggga	gctacagg	caacgat	ggtcctcc	actgca	tactc	tcaatacg	cgttcttc	cccactcg	gcaaaaac	atactcat	agcggat	ccccgaaa	Th.		caageeeg	ggcatcagag	gcattag	gtgcatg	cgccgaa	tcggcgatat
	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacggga gggcttacca tctggcccca gtgctgcaat 942	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacggga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacggga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 954	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 954 tgccgggaa gctagaagta gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 960	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 954 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 960 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 966	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 954 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 960 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 966 caacgatca aggcgagtta catgatcccc catgttgtgc aaaaaagcgg ttagctcctt 972	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 936 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 942 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 948 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 954 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 960 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 966 caacgatca aggcgagtta catgatcccc catgttggtgc aaaaaaagcgg ttagctcctt 972 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactcc 1978	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 960 caacgatca aggcgagtta catgatcccc catgttgtgtgc aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactccgt aattctctta ctgtcatgcc atcgtaaga tgcttttctg tgactgtgg 9840	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca aggcgagtta catgatccc catgttgtgc aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atcgttaaga tgctttctg tgactggtga 9840 tactcaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca aggcgagtta catgatcccc catgttggtac aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atcgttagaag tgcttttctg tgactggtga 9840 tactcaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900 tactcaacc aagtcattct gagaatagtg cagaacttta aaagtgctca tcattggaaa 9960	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctc agatttatca gcaataaacc agccagccgg 9480 agggccgag gccagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca aggcgagtta catgatcccc catgttggtac aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atcgtaaga tgctttctg tgactggtga 9840 tactcaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900 tcaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaaggat cttaccgctg ttgagatcca gttcgatgta 1002 cgttcttctg gggcgaaaac tctcaaaggat cttaccgctg ttgagatcca gttcgatgta 1002	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctc agatttatca gcaataaac agccagccgg 9480 agggccgag gacccacgct caccggctc ttatccgc tccatccagt ctattaattg 9540 tgccggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggtc 9720 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atccgtaaga tgctttctg tgactggtga 9840 tactccaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900 tcaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca gttcttagt tgacaccaact gatcttcagc atcttttact ttcaccagcg tttcttgggtg 10080 cccactcgt gcacccaact gatcttcagc atcttttact ttcaccagcg tttcttgggtg 10080	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag cgcagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagaagta gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtg cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca aggcgagtta catgatccc catgttggtatg gcttcattca gctccggttc 9780 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atccgtaaga tgcttttctg tgactggtga 9840 tactccaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900 tcaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca tcattggaaa 10020 cccactcgt gcacccaact gatcttcagc atcttttact ttcaccagcg ttcttgggtg 10080 gcaaaaaca ggaaggcaaa atgccgcaaa aaagggaata agggcgacac ggaaatgttg 10140	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacggga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaac agccagccgg 9480 agggccgag gccagaagtg gtcctgcaac ttatccgcc tccatccagt ctattaattg 9540 gctacaggc accagagta gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtg cacgctcgtc gtttggtatg gcttcattca gctccggttc 9600 ggtcctccg atcgtggtg cacgctcgtc gtttggtatg gcttcattca gctccggttc 9600 ggtcctccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atcgtaaga tgctttctg tgactggtga 9840 tactcaacc aagtcattct gagaatagtg tatgcggcag ccgagttgct ttacccgcg 9900 tcaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca gatcgatgta 10020 cccactcgt gcacccaact gatcttcagc atcttttact ttcaccagcg ttcttgggtg 10080 gcaaaaaca ggaaaggcaaa atgccgcaaa aaagggaata agggcgacac ggaaatgttg 10140 atactcata ctcttcttt ttcaatatta ttgaagcatt tatcagggtt attgctccat 10200	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag gccagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 gctacaggc actagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgttggtg cacgctcgtc gtttggtatg gcttcattca gctccggttc 9600 ggacctccg atcgttgtca gaagtaagtt gcccacagtg ttatcactcc tggttatggc gttcctccg atcgttgtca gaagtaagtt gcccgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgcc atccgtaaga tgcttttctg tgactggtga 9840 tactcaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct ttgcccggc 9900 tcaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca tcattggaaa 10020 cccactcgt gcacccaact gatcttcagc atcttttact ttcaccagcg ttctgggtg 10080 gcaaaaaca ggaaggcaaa atgccgcaaa aaagggaata agggcgacac ggaaatgttg 10140 atactcata ctcttctttagaa ttgaagcatt tatcagggtt cttgccctct 10200 agcggatac atatttgaat gtatttagaa aaataaacaa atacagagttc cgcccatt 10260 agcggatac atatttgaat gtatttagaa aaataaacaa atacggggttc cgccactt 10260	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgaa gctagaagtg gtcctgcaac tttatccgcc tccatccagt ctattaattg 9540 tgcctacaggc atcgtggtgt cacgctcgtc gtttggtatg ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9600 caacgatca aggcgagtta catgatcccc catgttgtgc aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggcgcaagg ttatcactca tggttatggc 9780 tactcaacc aattctctta ctgtcatgcc atcgttgtgc atcgttgtgc atcgttgtgc 9780 tcaatacgg gataataccg cgccacatag cacgcaggg ttatcactca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca tcattgggaaa agacggaata agggcgaacac agaaaggata ttgaaacttta ttgaaacatt tatcagggtt attgtctcat 10200 atactccata ctcttccttt ttcaatatta ttgaaacaa ataggggatc cgcacatt 10260 acccgaaaa atgtctaagaa aaataaacaa ataggggatac atatttgaat gtatttagaa aaataaacaa ataggggatc cccactctat acctttcatta ttgaaacaaa ataggggatac atcattagaa aaataaacaa ataggggatac atatttgaat gtatttagaa aaataaacaa ataggggatac atattttgaat gtatttagaa aaataaacaa ataggggatac atcattagaa aaataaacaa ataggggatac atatttgaaa aaataaacaa ataggggatac atcattaata atcattaaa 10320	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag gacccacgct caccggctcc agttaatagt ttgcccaac gtcattaattg 9540 tgcccaggaa gctagagta gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9600 ggtcctccg atcgttgtca gaagtaagtt ggcgcagtg ttatcactca tggttatggc 9780 ggcactgcat aattctctta ctgtcatgcc atcgttgtgc aaaaaagcgg ttagctcctt 9720 ggtcctcaacc aagtcatct gagaatagtt ggcgcaaga tgcttttcg tgactggtga 9840 tactccaacc aagtcattct gagaatagtg tatgcggcga ccgagttgct cttgcccggc 9900 tcaataacgg gataataccg cgccacatag cagcaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatcca gtctttggag 10020 ggcaaaaaca ggaaagacaaa atgccgcaaa acctttaac ttcaccagcg ttcttgggtg 10140 atactccata ctcttcctt ttcaatatta ttgaaagcat tatcaggggtt ccgcgcacatt 10200 accccgaaaa atgccgcaaa aaaaaacaa aaaagggaata catatttgaa gaattaaaacaa aaaaaacaa atactcctta ttcaatatta ttgaaagcatt atcatgaccat taacctataa 10230 aataggggt atcaccaata ctcttcctt ttcaatatta cgcgcacatt atcatgaacat taacctataa 10320 aataggcgt atcacgaaga cctttcgtct cgcgcacatt atcatgaacat taacctataa 10380 aataaggcgt atcacgaaga cctttcgtct cgcgccattatt atcatgaacat taacctataa 10380 aataaggcgt atcacgaaga cctttcgtct cgcgcgtttc ggtgaaaacct 10380	atcagtgag gcacctatct cagcgatctg tctattcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgaa gccagaagtg gtcctgcaac tttatccgcc tcatccagt ctattaattg 9540 tgccggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttgttgccat 9600 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca agggcagtta catgatcccc catgttggtgc aaaaaagcgg ttagctcctt 9720 ggtcctcccg atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttagtgg 9780 gcactgcat aattctctta ctgcaagagt tatgcggcag cacgttgtgt tatcactcgt tacttggaaa 9960 cccatcgtg gataataccg cgccacatag catcgttaat aaggtgctca tctaccagca tctaccagcg cacacagg cagaactgtt atgcgggaaac cttccaagga cttacaccgcg ttgagatcca gtcggggaaac cttacagggatca ttgagatcca gtcgggggaacc gatcttcag gggcaaaaaca ggaaagggaata cttaccgctg ttgagatcca gtcgggggaaac cttacagggaatca ttgagagccac ggaaatgttg 10140 ataccccata ctctccataga aaataaacaa atggcggacac ttgagaaccat tatcaggggtt cgccccactg acttttgaaa aaataaacaa ataggggttc cgccacttaa 10200 acccgaaaa gtgccacctg acttttagaa aaataaacaa ataggggttc cgccacttaa 10200 acccgaaaa gtgccacctg actttcgtct tgagagcatt tatcagggtt cgccacttaa 10320 aataggggt atcacgaggc cctttcgtc cgcgccttttc ggtgaaaacct 10380 aataggggt atcacgagg cctttcgtc cgcgcgtttc ggtgaaaacct 10380 ccccgaaaa gtgccacctg accttcgtc cgcgcgtttc ggtgaatacc taatttgaac accttcgtc cgcgcgtttc ggtgaaaacct 10380 aataggcgt atcacgaggc cctttcgtc cgcgcgtttc ggtgaaaacct 10380 tgaacacatg cagctcctgc agcttctgc cgcgcgtttc ggtgaaaacct 10380 tgaacacatg cagctcccgg agctctctgc agctctctgc cgcgcgtttc ggtgaaaacct 10380 tgaacacatg cagctcccgg agctctctgc agcttcttgc cgcgcgtttc ggtgaaaacct 10380 tgaacacatg cagctcccgg agctctctgc agctctctgc cgcgcgtttc cgcgcgatcc cgcggagcag 10440	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcga gacccacgct caccggctcc agattatca gcaataaacc agccagccgg 9480 agggccgag gacccacgct caccggctcc agattatca gcaataaacc agccagccgg 9480 tgcctggaa gtagttcgcc agttaatagt ttgcgcaacg tctataattg 9540 gctacaggc accgtggtg cacgctcgtc gtttggtatg gcttcattca gctccggttc 9660 caacgatca aggcgagtta catgatcccc catgttgtgc aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggcgcagtg ttatcactca tggttatggc 9780 gcacctgcat aattctctta catgatacgc atcgttaaga tgcttttcg tgactggtga 9840 tacatcaacc aagtcattct aggaatagtg tatgcggcga ccgagttgct ctgtccggcg cacctgct ggaaataccg catcataggag cagaattcc ttaacaccaggt ttgagaaccggtga 10020 cccactcgt gcaccaaca tctaacggag catcattcact ttaactagaa aggaggaaca atgccgcaaa aaagggaata ttgaaacct ttaaccagggt ttttagtggt 10180 atactcata ctcttccttt ttcaatatta ttgaaagcat tatcagggtt cgcgcacatt 10260 acccgaaaa gtgccacctg acgtctaaga aaataaacaa ataggggttc cgcgcacatt 10260 aataggggta atcacgaga cctttcgtc tgggaacact taacctataa 10330 aataggcgt atcacgaggc cctttcgtc cgcgcgtttctgtc ggtgaaaacct taacctataa 10330 aataggcgct cagggagcac agcttctgtc taaggggttc cgggaacact taacctataa 10500 caagcccgt cagggcgcgt cagggggggtc taagggggtgt tggaaaacct taacctataa 10500 caaaccattg cagggcggt tagggggggt tggaggggttctcgcg ttaagggggtgt taagggggtgt taggggggggttctcgcg tagggggggttctcgcg taagggggtgt taaggggggtgt taaggggggtgt tagggggggttctcgcgggggggggg	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 acceptegg tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcgg gaccacgct caccggctcc agatttatca gcaataaac agccagccgg 9480 agggccgag gaccacagt gtcttatccgcc tccatccagt ctattaattg 9540 tgccgggaa gctagagtaa gtagttcgcc agttaatagt ttgcgcaacg ttagttgccat 9600 gctacaggc atcgttggtc cacgctcgc attgttgtgtag gactcattca gctccggtc gtttggtat gcttcattca gctccggtc gtttggtat gcttcattca gctccggtc gtttggtat gctccatcag atcgttgtca gaagtaagtt ggccgcagtg ttatcactca tggttatggc 9780 gccactgcat aattctctta ctgtcatgcc atcgttagaga tgcttttctg tgactggtga 9840 tactccaac aagtcattct gagaatagtg tatgcggcga ccgagttgct ctgcccggc 9900 tccaatacgg gataataccg cgccacatag cagaacttta aaagtgctca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatca tcattggaaa 9960 cgttcttcg gggcgaaaac tctcaaggat cttaccgctg ttgagatca gtcgatgta 1020 gccacatag gaacgtcaaa aaagggaata agggcgaca gtctgatgt 10140 atactcata ctctccttt ttcaatatta ttgaagcatt taccagcg ttactccat 10200 accacactg acctccatttagaa aaataaacaa ataggggttc cgcgcacatt 10260 acccgaaa atatttgaaa aaataaacaa aaagggaata atagggggtg ccttcgtc gcgcgcttc gcgcgcttct acccgaaaa ctctccttt ttcaatatta ttgaagcatt atacctataa 10320 acccgaaaa atatttgaaa aaataaacaa aaaagaggatt ataacctataa 10320 acccgaaaa atatttgaaa aaataaacaa aaaagaggatt ataacctataa 10320 acccgaaaa catatttgaa aaataaacaa aaaaaaacaa aaaagagggtt cgggggcggt cagggggggggg	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 cccgtcgtg tagataacta cgatacgga gggcttacca tctggcccca gtgctgcat 9420 agtaccgcga gaccacagct caccggctcc agatttatca gcaataaacc agccagaccgg 9480 agtgccggag gtcctgcaac tttatccgcc tccatccagt ttgcgccaacg 9540 gctcacagg gtcctgcaca gtttggtaatgt ttgcgccaacg ttgttgccat 9540 gctacaggc acctgagtta catgatcccc atgttggtag gcttcattca gttgtgccat 9720 ggtcctccg atcgttgtc acgcagtt gctccattca tgttgccct 9720 ggtcctccg atcgttgtc acgcagtg ttatcactca tgtttatgcc 9780 gcactgcat aattctctta catgatccc catgttgtgc aaaaaagcgg ttatcactct 9720 ggtcctccg atcgttgtc acgcagtg ttatcactca tggttatggc 9780 gcactgcat aattctctta cggaaatagtg tatgcggcga ccgagttgct tatcaccg ggtcagaca catcgttgtg tatgcggcgg ccgattgtg tatgcggggg ccgttctctg gggcgaaacttta aaagtggtct ttacacagg gataataccg caccagag cttaccggg ttgagaacg gggaaacttta aaaggggaata aaaggggaata aaaggggaata aaaggggaata aggcgaacac ggaaatgttg 10180 atcaccaga ggaaaggcaaa atgccacaag acctttaact ttcaccagggt ttgagaacgtt attgtctcat 10200 agcggaata atcttcata ttgaagcat tatcagggtt cggcacatt 10200 agcggaata catcttgaa aaataaacaa ataggggttc cggcacatt taccagaa ataccacta atattgaaa aaataaacaa aaaagggaata accattat atcagggttc cggcacatt taccagaa ataccacatg agcaccccgg agacggtcc cgccattat atcaggagccgt tagagcgcgt tagagcgcgt tagagacccgt tagagcgcgt caggggtgc cgttctctct agggcgccct tagagcggtcc cggaaggccc catatcgac gcttccctt tagagacccc 10500 gcatcagag agcacgttga agccgttga agccgttga agccgttga agccgttga accattcgac acctcctt tagagacccc cgaaaggaat 10500 gcatcagag agcagttga agccgttga agccgttga agccgttga agccgttga agccgttga agccgttga agccgttga 10500 gcattagga agcagttga agccgttga agcc	atcagtgag gcacctatct cagcgatctg tctatttcgt tcatccatag ttgcctgact 9360 acceptcgt tagataacta cgatacggag gggcttacca tctggcccca gtgctgcaat 9420 ataccgcgag gacccacgct caccggctcc agatttatca gcaataaacc agccagccgg 9480 agggccgag gcagaagtg gtcctgcaac tttatccgc tccatccagt ctattaattg 9540 gctacagag cgcagaagtg gtagttcgcc gtttgatagg ttgctgcaacg ttgttgccat 9660 caacgatca aggcgagtta catgatccgc gtttggtgg caaaaaagcgg ttagtcctt 9720 ggtcctccg acgttggtc aaaaaagcgg ttagctcctt 9720 ggtcctccg atcgttgtca gaagtaagtt ggcgcaaga tgcttcattcg tgactggtg 9840 tcaatcaacc aagtcatcc catgttgtgc accgttgtgc ttatcactca tggttatggc 9780 gcactgcat aattctctta ctgtcatgc atcgttagga tatgcggcga cagaatacg gataataacg caccatagg cagaacttta aaagtgctca tcattggaaa 9960 ccacatagg gggcgaaaac tctcaaggat cttaccggt ttgagatca tcattggaaa 9960 ccacctcgt gataataccg agccacattg ttagcggcaca ggaaggcaaa atcttttaga aaagggaata agggggaaca cattttgggt 10020 gcaaaaaca ggaaggcaaa atcttcaaca aaaagggaata agggcgacac tatttgggtg 10080 atcccactcat ctcttccttt ttcaatatta ttgaaagcat tatcagggtt attgtctcat 10200 agcggatac atatttgaat gtatttagaa aaataaaca ataggggttc cgccacttat tgaaagcat taccagacg cagttcttgc aggacgccct caggggcgcccg catttcgtc cgcgcgtttc gggggacacact taacctataa 10300 aataggcg cagttcttgtc cgcgggttc cgggggacccgc caggggcgcccg caggggtgt cgggggcggtt cagcgggttc cgggggcgcgc cagaaggac ccattcggt cagcggttc cagcgggttc cagcggttg aggccgctccct atgcgaaccc 10560 gcattcaga agcagcccag cagattgta aggccgttga gccctccttagcc cactatcgc cagcgcttga agccgccgc cacataccc 10680 gcattcagaa aggagcccag caccataccc 10680 gcattagga agcagcccag tcccagacc cagagcccgcccgcccggccccggccccggccccggcccccc	atcagtgag gcacctatct cagcatctg tctatttcgt tcatccatag ttgcctgact 9360 atcagtgag tagataacta cgatacggaa gggcttacca tctggcccca gtgctgcaat 9420 ataaccggag agacccacgct caccggctcc agattaatca gcataaacc agccagccgg 9480 aggggccgag gccagaagtg gtcctgcaac tttatcaact ctattaattg 9540 gctacagggc atcgtggtgt cacgctcgtc gtttggtatg ttgccacagt ttgttgccat 9540 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg ttgccacacagt ttgttgccat 9540 gctacaggc atcgtggtgt cacgctcgtc gtttggtatg gcttcattca gctccggttc 9780 gcactgcat atggtgtca catgatccc catgttgtgc aaaaaagcgg ttaccctct 9720 ggacctccc atcgttgtgc atgattgcc tractaggtg 1000 gcactgcac atcgttgtc atggtgtggt gatcgtctcc agattgtcacac atggttgtgc atggtgggg acceptact atggtgggggggggggggggggggggggggggggg

16/39

gtgcggaacg gcgttaccag aaactcagaa ggttcgtcca accaaaccga ctctgacggc agtttacgag agagatgata gggtctgctt cagtaagcca gatgctacac aattaggctt gtacatattg tcgttagaac gcggctacaa ttaatacata accttatgta tcatacacat

17/39 Construction of pSFVlink



SUBSTITUTE SHEET (RULE 26)

FIG.6/

Nucleotide Sequence of pMP76

140 080 200 1380 1020 260 540 009 720 780 900 960 420 480 099 840 360 gaccgtcatg gtgtcgtacg atcgctgtac caccccgttt cggttttggc ctccacccca aaatgtcgta gtctatataa caaaagattt ggccgccaaa ggcatttccg cagagcattt catcttggat cgtatgccct ggcagcggcc cgacgagcag cgggactttc atagtaatca acttacggta atgacgtatg tatttacggt cctattgacg ttatattggc atgcaccaac ggtttgacac ggactttcca cacccacgat ctttgcagaa atgcaaatgc aagacacact aataccactg caaagaaact ccgacctgca cagacgtcac caaactgggc acggtgggag tacacgacgc catggtgatg atttccaagt aagtccgccc catgacctta atatgtacat ctagttatta gcgttacata gacgtcaata atgggtggag atgtgtgaca ttcatcaagt gagactgaca gatagctacg ggaaaaatca tgcctgcata atgcccagta tcgctattac actcacgggg aaaatcaacg gtaggcgtgt agagattaac ccaaatgacc tctacgcaca tatgctgtac tattggattg acctacgcca atcatatgcc tgattattga atggagttcc cccgcccatt attgacgtca ctatatcata cgaaaggctc ccaggacgtg tgacagccca gcaggtcaca gatcgagcag gagaatgatg agagategea tcctaccttt cagaacggcg cgcgtatcca gggactttcc gtattagtca tttggcacc caaatgggcg cgtatggcgg ccgctacgcg atgttgacat tagcccatat catcaagtgt gcctggcatt ageggtttg tacqttgtat cccaacgacc acgctgaatc gtacatctac tggagtcatt cagaagaccc tggccgtata tgaaaggtgt cgctagcagg ggccattgca tatgaccgcc cattagttca ctcgtgaccg aacgccaata cttggcagta taaatggccc tgggcgtgga tgggagtttg cccgttgacg tttagtgaac cctgccacct atattgaggc ctaccaaatt cgccttccag tgctggatag tcgttcgagg tegeacetgg aaactgccca ataacccgc gcagagctcg tgttccagct gtgcatgttg atcggcagtg atgcgcagcg tccgggaagg gctacgccag catcaggcga tgtttgacg attggctatt tcatgtccaa aatggcccgc ttcccatagt tcaatgacgg ctacttggca agtacaccaa ttgacgtcaa gcagccgaag attacggggt

18/39

=1G.6E

19/39 21000 2160 2160 2460 2220 2280 2520 2580 2640 2700 2760 1740 1800 1860 1920 1980 2040 2340 2400 1500 1560 1620 1680 gggagtcgtc aacacctcgc cgtagttctg agcagagcag atatgacggc ttgagcgag ccatattgcc agctgaaaga agaggaagcg cgcctacgaa agtgaaggtg cgcaatccca aatacctgtt ggaggccgag ctttggggtt atcatgtgaa gaactatctg agaccttgat gtgggcattt aagactcggc gttctcggta accetecgta ggtagggtac tgtcaaagga tcaaatgact gggattgaat agtttcaagc ggaaactata ccatctgtga gggtcytgga taggaaatta aggtcgacgg agaaagtcag tagtaggagt tgactgaggg acacagtcat ataccatcgt acggtaaaac ccacagacac agttgttagt acacgatgaa aatacaaggc cccagacaat ctacaggcct agcgagagtt aggagaggtt cggcggagac tgcaccctct gcgtcaagag tccatyaatt gctggcactt gctgctgctt cgaaacacta cccatcgcgc gacgtactac ttggccccg ggcggttacc ttcgtcaaca gagaactacg aacccccgt ctactgagga cccggcctgt gtgtgcaaga gtcccctcaa gacgcacaga tgggcgaggg tcacttactt aaaccagaca agcctatggt aagaagacca caagaggaga gcaggtgcag ccggtccctg aagactacag gcagcatcct aaaccttgcg tgtaggtgcg caccgacgag agagctaacc ggcaccatat ggatgctgaa accetegte agagtatcac acagccgaac cgggaggcc ateggecatt cgaaagggag cgacgtagat gagctccaag aggactgtgt gaagcaattg gagcagaaag atcctttacc cactatgtgc gggattccta atgcacctac cacaccggag aagaacacag atttagcaag ccgagagagg catgtacaag cgtcatcccg gcttttggcc aagtcaccgc taacacataa tggtgtacaa cgtcgctgaa agtacgtgtt tgttggtggg tcaggccgtc aagccttacc ttgaagaact ccgtgctcaa taccatgtgg ttctccgcaa aaggtaaaca atcacgcgga ttgtgaacgg tggccgtcgc ctctgggtgt agatgcacac ttaactcgtt cgtcagccag ccaggaacat tgtacactga ttaagaaat cattccctgt cgaccgacgt gcattaagat gtgaaaataa agcgccacta gacgtcgacg agcgcgttga tccccgcaga agggtcctac gttcacggac actgacgccg gggctgaaga gtgttacagg ttccacctga cttccgattg gatgaaaac aaaacgagga ccttcagagt gtcagatcac ctcgacgcgt ctgactagag tegggtttgg aaactgtcca ggatctacat gggtacgtag gccgtgacgt gaaagagtct ggcatactag cagaggatag

<u>16.60</u>

gcaagtctgc	tattattaag	gcct	caaacacg	ctggtcac	$\frac{1}{2}$
b	gaaa	ttaacgac	aagaa	cdcdd	9
D	tgactccatc	taaac	gtgtcgtc	gccgtgga	12
Ü	tttcgcttgc	attccggt	U	tgc	8
	agtggtgtta	ga	ccaagcaatg	gattctt	24
	aa	acaacatc	actgaag	tgt	30
	tcca	gcca	gtctacgt	cac	36
	ccgtg	aacccata	ata	caggaca	12
	gt	acatgcttcc	aggctgg	aagcagct	48
	aagtcat	gcagca	atctcagg	cctcacccgc	54
	cagaagg	atga	cttgtat	Jtc	900
	acgcgcac	ggatagg	tggtgtggaa	ggc	99
	gtttggg	cccttgat	ttctttc	tttcgctatt	720
	agagac	ttcagg	tgttgtttag	aag	78
•	ccct	aattttgt	ctttcac	ctg	84
	ttttctt	cattttc	act	ttaaactt	3900
	tttaaatt	gtt	tttgt		96
	aggc	agggtata	atatt	tcagcaca	02
	taaat	taaggtagaa	tctgc	tataaattct	80
	ttggta	acaact	cctggtc	atcctgcc	14
	atatacactg	gagat	ggataaaata	ctctgagtcc	20
	ttca	ccttcttc		ggtcctatca	26
	tacggccaca	ttggaagaat		acacgacaaa	\mathcal{C}
	ctgc	tgtggac	cgttccagaa	agc	4380
	ctg	ctggacactg	gaatca	attgacagca	4440
•	tacagcattt	aaggaggaca	gagcttactc	tccagtggtg	4500

PCT/CA98/01065

FIG.6[

5220 C 5280 C 5340 5580 5640 5700 5760 5820 5940 0909 5040 5160 5400 5460 5520 5880 4620 4860 4920 4980 5100 4740 4800 680 cacgactgaa agtaaacaga cggcggaaga ggacgctgac cattgacatg ggtgagagtg gtcgctgtac accetetacg gcacacggcc agaagcggct ggccgtggcg taaaacagtc gatactgacg gggcgaaaca cgaagccgtt ttgtgtcacc ggctgagtac gtaccacgic ggctgacgcc ccactaccag acgactgcta cctgttttct tggtggaagg cttcctgaag accgctttct gttgtcaccg tggccgccga gagtgttcag tggacgccac ccacagactt atatggcaga atttctctgc tccaggaagc ccactgacgg tatacgcgct tcagaatcca ataaaatcag tgcgcccgga acggaaagag gagaagccat ccacgtgcac gcgtatgcag tgggcacaat ataacagacc ctagacatac gaaaaatcca acgccctggt aagtaagagg taggactgcc gagatgcgct tggacagtgg gggtcacttg taccgggcag gtggagctga ggctacagta gctgctattg cagatatgcc gtagcgccta ctgtccacag ttcacagcaa gagaagaaaa aactttgaca ggatacgccg gcaagagtgt gtgtatgccg gcagacatag gtaggggatg gcaacaccag ggagttgacc aaccactggg aggctggaag atcgcagaaa aggctgccgc ctggtcaata cctcgacgca gacctaagtt cacacggaat atgcttgggg caagggagca catccacgct ggccgctgtc catcccgctg caaccatcta caaaagttgg caatgatgac gggtcgtaag attcaaccag ggcaaacgaa gctgttctcc gctgagtgcc agttaagaga ggttgagtgg taggtgctac gagagettae ccgtggaact cctggctttg tgtgaacatt gaagctgcag gttctcgtct caagtactat ttacgagaac aacagctgcc gcaggcagtt tatcaaccgc cagctaacgc gcagcgtagc agcaatccct actgcagaga tggagttgct gcagcctggt aaggtacgaa gactgcaaga cgtcagcctt cgtaccccgt accgcgaatt tcaatgccgc taagcagaaa aagtgttctt tgaataccaa catcctacag tgtccctgta atacgggcaa atgtaattcc gtgagtacaa caggcgccga acttggtctt accacgccat gcatcttgat aaatttgcac aaggcagtag gggtgtgcac gtggttaacg aagaaatggc tgtgcggct gcggaagggg ctgtcactga gataggctgc gtgaccatct aggacggctg cacccggaca tegtactttg tgtggccca ctgctggtga cagtgtgtcg gttcctcct ctacaccaga gccttgaatg gcccgaagg gtgctggaca aagacggtta ctgaatgtca ggcaggttcg agcaatacag atgtatggat gggcagtggc aaacccggcg

6780 0069 7020 7080 7140 7260 7320 7380 7440 0969 7200 0999 6720 6840 6240 6300 0099 6360 6420 6480 6540 gaaacatcat cacactacag agaactaccc ctccggagaa caacttggtt acaaaaatcc gaaaatgtac ccgcatacca aagattctca cccaacagty cgggtcggat cactacctat gcgactaggc gatgcaccca agccacggtg gcacctgaa gacgcctgcc cgagcacgag ccttaggtca accttcagtg gtcgctaccc agtagtgacg gagagctgca acctcccagg gttacgaggg ccatgtagat acatggttga ccgtgatcga ggtgctaccc cctttcagaa cgcaaatgcg gctatgcctg ctaagaccca agaacatgaa ccagaaatta ctgagaacat cagatcggtc cgagaaagcc gcgactttga acgacgtcct gacatttaca tccaggagga tgaaaatgca cggacgtagg cggcagatgt cgcgcccgaa acccgacggt gcgataccat tggctcccat attcatcaac tcccgaaata ggatcgcccg gtcccgtcac tgcaacgtca tgcttcaagc gcatacttgg gcgaagctcc cggataacca tactccccta gaatacctat gccttgttcg attectecae ttgacgttcg actggcagcg ctgttgctgc cgcaaagtgg cacagggag gcggacctgg gtgccggcgc ggagacttcg ctggatgcgg ctcctgttcg acggaccact tccactgcca tacgagccaa aacgattccg acagcagaac tettteece tgaatacgac attctgcccg acgcagtgcc caagagaaac caacgtggag acaacctatc gaaagctgct ggccagattg agcgtgcaac ggagcgaccg caagctgcct gattactttc ctcctcggac gtgcgcacaa gagggagaag ataccagtct ccgccccgtg cgactcgatc cgcaggcatc cgagaacccg atgtccggtg ggtttgctca cgagaaggtt cgcatctacg cgactcgtct ctacgcaatg agataacaga agccgactgt cggccgccac cggcagtgtt ttcggtaccc tagcaatcgc acagagcgac aatatgctaa tgaaaggccc acaatctcca tggatactga tcacatcggg acctgaacc cccdcdcddc tggcctccgg ataagagtcg tcagatccaa actggaccac atgtggacct cgtttaggaa catatattt gcctgtgccg aaagcatggt ggaagtatgc cgtgtgacat aggtaaagtg gtggacaggc agccccgatg gcgtcgtacc agttgcttgg gcgtaccacc aacgtgctag accatggact tattgggaag teggaggeta acatacgcgg gtgaccaaat cgcgcgggtg gttaggcagc ccgccaaaat gctgacgtac cccgcagacc taccttgcct gtcgatgcgt atggacaaca caccaagtta ggggtgcaga gttagtccgc tttgacttgg agtttgcagt ccaaggactg acagtgccct

22/39

										_		20													
χ	74	30	36	32	98	04	10	16	22	280	34	400	46	52	58	64	70	9/	82	88	94	00	0906	12	18
aaagt	gcagcgg	taaatgc	gacgcgat	atcattcgac	ctaggggt	tgtcacct	ctgactt	agactcac	ctccga	attge	ag	agc	gt	atga	aaggcgtt	ata	gtaattaatt	cddcddcccd	gc	caattgctcc	aaacgcagcc	ccgacaagaa	tatct	gcactatcat	ctggtgctgg
gaaacga	aattc	agtaagg	aagact	ggacattg	ctcgaag	aatatcc	ggcatgt	actggagc	tcacgga	ga	agtttttg	caagtt	gagtgac	ct	gagggac	tagattg	atccc	gcccgcg	cccgacttcc	agacagaacg	ccaaagccga	acaagcaa		gtcgggcacc	ggcgctat
ccgac	caaagtc	cacagggaat	atatgtcg	ctagag	Ţ	cctttggg	atgaaa	caagcagg	acaacatc	tcaaca	ggggattc	gc	ac	aggtgg	caccttg	acggcggt	ata	cgccggt	tcgt	gctgacaatg	gacaaccaaa	aaga	gcatgaa	tccagaca	ccttcgcaat
gacagatt	gaggaag	tgcggc	cacattgttt	aga	gctcttac	atcgagg	ttcggagc	atcaccat	atcggcg	D	atttt	acccact	aagaca	ccgaact	atagccat	atacacct	gcgcact	gttttacg	ccggtg	ccgtaaatgc	agaagaagaa	cgcagcagca		gtg	tgggg
aggttccca	gaaacaca	cgctt	staacgtg	acttccacc	acgactcct	gf	gcgc	tgttttga	gtgcggcctt	ggagaggt	aaaacc	gaagtgttta	caagcag	caggcttggg	agtatcc	aggac	gatc	O	tgca	catcagc	cccaaaccaa	aacggaaaa	aaa	ğ	aatctcgggt
ccgctgcagg	actccaggga	ccattggcga	gtgttacgcc	tag	aaaagccagg	gatcagtacc	caac	tta	actccg	agctg	tgggc	agaccgcc	cago	tggttccgga	agge	aaattg	cagaat	tacat	ccttg	atgcagca	tgctaggcct	caagaagatc	gaagaagaaa	gtatgcgg	gggtgcagaa

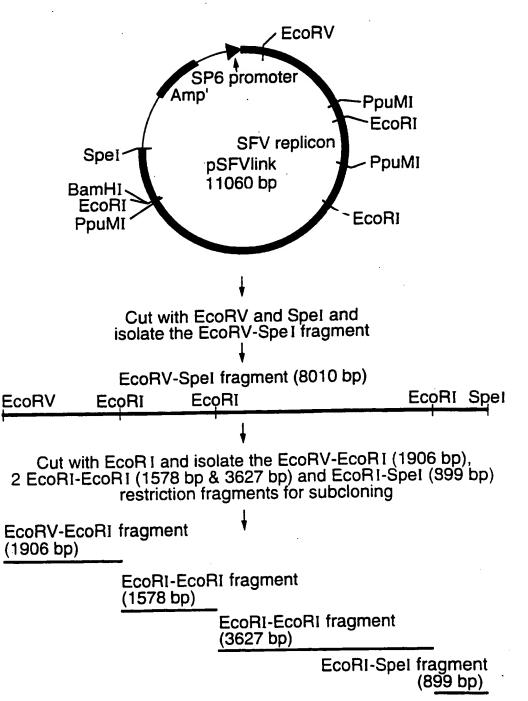
						24	4/3						_	_	_	_	_	_	_	-	_
9240 9300 9360	42 48	54	200	9720	8/2	34	2	960	002	800	014	020	026	0	038	044	020	056	062	990	10740
attgatatag taactgtata tcacqqaaac	aagcttaa	aaaaaaaa	gaaggagg	gccagccarc	tattctgg	gcatgct	gaacaaaa	tcccttt	gtgaa	agcctggg	u	ggcggtt	cgttcggc	atcag	taa	aaatcgac	tacacat	gtccgcct	tcagttcggt	Ŭ	tatcgccact
aggcaatggc catataacca qtqqtccqcc	aagcttac	e ceaacae aaaaaaaa	ctgggcat	acycicyayi ggtgccactc	ggtgtca	acaatago	tactgcc	ccagcttt	tgtttcct	taaagtg	cactgccc	მამამამ	tgcgctcg	ccac	ccaggaac	agcatcac	taccaggcgt	ccggatac		cccgttcagc	agacacgact
aagttagggt taagcaatgg aattagccc	caataatt	ycaactyy aaaaaaaa	geggteeg	O	ctgag	gattgg	ggtaa	aggtggag	gtc	gccggaag	gttgcg	aatcggccaa	g	ggtaatacgg	caaaa	ccccctgac		ctgcc	tagctcacgc	gcacgaaccc	caacccggta
ctccgcagat aaagttaggg	gacceses Cattaatt	LLALL aaaaa	ccacctcc	taagggagat tqccttcctt	ttgcatcgca	gggg	ctcgacc	agcctagttc	tggcgtaatc	caaca	tcacattaat	tgcattaatg	cttcctcgct	actcaaaggc	gagcaaaagg	taggete	acccgacagg	ctgttccgac	cgctttctca	tgggctgtgt	gtcttgagtc
tgc aaa	catattga	ם מ	catggcat	ctcggatggc ccctcccccq	atgaggaa	ggcaggac	gctctag	acgccatgcc	tttcg		tgagc	cgtgcc	gctcttc	tcagct	agaacat	Ö	gtg	tgcgct	aag	gctccaa	taacta
tgtggtca aagaaaat	ggggcaa	Cga	aacgggtc		tcctaa	ggtggggt	gatgeggt	atgatcct	tgagggtt	tatccgct	gcctaatg	ggaaacct	catattgg	cgag	aacgcagg	gegitget	caag	ageteect	teeette	taggtc	

agec actggtaaca ggattagcag agcgaggtat gtaggcggtg ctacagagtt yitgg tggcctaact acggctacac tagaaggaca gtatttggta tctgcgctct yeca gttaccttcg gaaaaagagt tggtagctct tgatccggca accaaaccac tagat cctttgatct tttctacggg gtctgacgct cagtggaacg aaaaactcac yatt ttggtcatga gattatcaaa aaggatcttc acctagatcc ttttaaatta yatt ttggtcatga gattatcaaa aaggatcttc acctagatcc ttttaaatta yatt ttggtcatga tatatcaaa acttgagtaa acttggtcg acagttaccac yatt ttggtcatga tatatcaaa acttgagtaa acttggtcg yatc agtgaggcac ctactcagc gatctgtcta tttcgttcat ccatagttgg yatc agtgaggcac ctactcagc agaaagtgag ggagccacgg ttgatgaga yatc agtgagaccag ttggtgattt tgaacttttg tttgccacg gaacggtctg yatcggaccag ttggtgattt tgaacttttg ctttgccacg gaacggtct yatga aggtgaccag tctgatct tcaactcagc aaaagtcga yacg tcccgtcaag tctgatct tcaactcacg attattcaa yatcg tccgtcaag tctgatat gctctgccag tgttacaacca yatga aaaaactcat cgagcatcaa atgaaactgc aattattca tacaacaacaa yatga aaaaactcat cgtcaaaaacg attatgcatt tctttccaga cttgttcaa yatga attcccct caccaaaatc actcgcatca accaaaccgt tattcattco yacc tgagcgagac gaaatacgcg atcgctgtta aaaggacaat tacaaaacag yacc tgagcgagac gaaatacgcg atcgctgtta aaaggacaat tacaaaacag yacc tgagcgagac gaaatacgcg atcgctgtta aaaggacaat tacaaaacag yacc tgagcgagac gaaatacgcg atcgctgtta aaaggacaat tacaaacag yacc tctaatacct ggaatgctgt ttcccgggg atcgcagta yacc tctaatacct gaaatactgt tttcccgggg atcgctata yacc tctaatacct gaaatactgt ttcccgggg atcgcagta yacca tcataatacct gaaatactgt ttcccggggg acgatca yacca gaagtacgga atcgctgttacca acaaaccgt tattcattco yacca gaagtacgga atcgctgttaca acaaaccgt tattcatcatca yacca aaccggcgca aacaggcgcatca acaaacaacaa yacca accagacgca atcgcatcaaaatcaacaacaacaacaacaacaacaacaacaac																										
agec actiggtaaca ggattagcag agegaggtat gtaggeggtg ctacagagtt yieg tggectaact aeggetacac tagaaggaca gtattiggta tetgegetet yeca gttacetteg gaaaaagagt tggtagetet tgateeggaa aaaaaggate taget ettetaacggg gtetgaacgt cagtggaacg aaaaactcacg yatt ttggteatga gattatcaaa aaggateete actiggtea yatt ttggteatga gattatcaaa aaggateete actiggtea yatt ttggteatga gattatcaaa aaggateete actiggtea yatt ttggteatga gatetgteta tttegtteat catagitea yate agtgaggaac cataccage gatetgteta tttegtteat catagitea yate agtgagcac teatecage gatetgteta tttegtteat catagitea yate agtgagcac teatecage agaaagtgag ggaacacgg ttgatgagag yate ggtggaccag ttggtgatt tgaactttg etttgecacg tratteacac yate agtggaccag teggeateete tgaacacteac aaaagttega yate aaaaactcat cagacatca atgaaactge aatttatca yate aaaaactcat cagacatca atgaaactge cattagacga yate aaaaactcat cygaaacacag tettgaatgaa ggagaaaac yate aaaaactcat cygaaaaaa aaggttatca agtgaaaaac yate atttecet cyteaaaaat aaggttatca agtgaaaacc yate tecgytaga atggeaaaaat aaggttatca accaaaccgt tattcatteg yate tecgytaga atggeaaaaat aaggttatca accaaaccgt tattcatteg yate accggegaa gaaatacgeg atcgetytta aaaggacaat tacaaaacagg yate tecgyteaga atggeaaaat aaggttatca accaaaccgt tattcatteg yate aaccggegca gaaatacgeg atcgetytta aaaggacaat tacaaaacagg yate aaccggegca gaaatacgeg atcgetytta aaaggacaat tacaaacagg yate tetaatacct ggaaatacgt ttteccgggg atcgcatca yate agaatacgt tatteccgyaa agaatacgga atcgcatca accaaaccgt tattcattec yate tetaatacct ggaaatacgt ttteccgggg atcgcatca yate agaatacgt tatteccgyaa atcgctatta aaaggacaata tacaaacaaggacaatca accaaaaccgt tattcattcg yate tetaatacct ggaaatacgt tattcgcaga accagacact tacataacca yate agaatacgt tattcccgyaa accaggacatca accaaaccgt tattcattcg yate tetaatacct ggaatgctgt tattccgyaa accagacact tacataacca yate agaatacgt gateggaacact aacaaccgt tattcattcg yate agaatacgt tattcccgyaa accagacaccacacacacacacacacacacacacaca	80	98	92	98	04	10	.16	-22	28	34	1400	1460	1520	1580	164	170	176	182	188	194	200	206	212	218	224	230
agec actggtaaca ggattagcag agcgaggtat gtaggcggtg yttgg tggcctaact acggctacac tagaaggaca gtatttggtg ycca gttaccttcg gaaaaagagt tggtagctct tgatccggc aget cctttgatct ttctacggg gtctgacgct acgggaac yatt ttggtcatga gattatcaaa aaggatcttc acctagatc yatt ttggtcatga gattatcaaa aaggatcttc acctagatc yatt ttggtcatga gattatcaaa aaggatcttc acctagatc yatt ttggtcatga gattatcaac yatt ttggtcatga gattatcaac yatt ttggtcatga gattatcaac yatt ttggtcatga gattatcaac yatt agtgaggcac ctatctcagc gatctgtcta tttggtcac yatc agtgaggcac ctatctcagc gatctgtcta tttggtcac yatga agtgagcac ctatctcagc gatctgtcta tttggtcac yata agtgaaccag ttggtgattt tgaacttttg ctttgccac yata agtgaaccag tcatgatct tgaacttttg ctttgccac yatga aaaaactcat aaagccgttt ctgtaatgaa ggagaaaac yata aatttcccct cgtcaaaaat aaggttatca yata atttcccct cgtcaaaaat aaggttatca yaaa tccggtaacaaaa attgaaactga yaaa tccggtaacaaaa attgaaacac yacca ttacgctcgt catcaaaaat aaggttatca yaaatacaaaat aaggtaatca yaaatacct ggaacactgc catcgcatca accaaaccg yacc tgagcgaaa tagcaaaaat aaggttatca accaaaacg yacc tgagcgagac gaaacactgc catcgcatca accaaaccg yacc tgagcgagac gaaacactgc tttcccgggg atcgcagta yacc ttaatacct ggaaacactgc tttcccgggg atcgcagtca yacca gagagcactct catcaaaaat accagaaccc yacca ttaccaaaatc gaaacactgc catcacacca yaccaacactcc catcaaaaat aaggtcatca acaaaccc yacc gaacaccgc ttccccgggg atcgcagca yacatcatct catcaaaacc accagaaccc yacca gaaacactgc atcacaaaacc accagaaccc yacca ttacgctcct ggaacactgc tttccccgggg atcgcagca yacca gaacacctgc catcaaaacc accagaaccc yacca gaacacctgc catcaaaacc accagaaccc yacca ttacgctccct catcaaaacc accagaaccc yacca ttacgctccct catcaaaacc accagaaccc yacca ttacgctccct catcaaaacc accagaaccg yacca ttacgctcct catcaaaacc accagaaccg yacca ttacgctccct catcaaaacc accagaaccg yacca ttacgctcccc accaaacccc yacca ttacgctcccc accaaacccc yacca ttacgctcccc accaaacccc yacca ttacgctcccc accaaaccccc yaccaaccccccc accaaaccccccccccccccccccc	tacagagtt	ctgagatat	acaaaccac	aaaaggatc	aaactcacg	tttaaatta	cagttacca	catagttgc	ctgactcat	tgatgagag	aacggtctg	ttattcaac	attaaccaa	atcaggatt	accgaggca	aacatcaat	accatgagt	ttgttcaac	attcattcg	acaaacagg	acctgaatc	gagtaacca	ttccgtcag	gccatgttt	cacctgattg	tggaatttaa
agec actggtaaca ggattagcag agcgaggtatggg tggcctaact acggctacac tagaaagact tggtacctcd acggctacac tagaaagactcgaac gttaccttcg gaaaaagagt tggtagctctgaac gttaccttcg tttctacaga gcagcaactcgaat ttgatcatga gattatcaaa aaggatcttcaact attgaggtaactcgagt tttaaatcaa tctaaaagtat atatgagtaaactg agttgaaggacac ctatctcagc gatctgtctaactg agtggagcac ctatctcagc gatctgtctacag aatcgcccaa tcatccagc agaaagtgagggg agtggaccag tcatccagc agaaaagtgaactaga aatggcaacag tcagcgtaat gatctgctagaccag tcagcgtaat gatctgccaaca atgaaactgaacca tatttttgaa aaagccgttt tgaactttttgaa aaagccgttt ctgtaatgaacca tattttttgaa aaagccgttt ctgtaatgaacca tattttccct cgtcaaaaat ctgtaatgaatgatt aatttcccct cgtcaaaaat aaggttatc cgcaaaaat cattgcaacaca tcagcaacaaaaccaaaaccaacacacacacacacacaca	taggcggt	tatttggt	gatccggc	cgcgcaga	agtggaac	cctagatc	cttggtct	ttcgttca	gaaggtgt	gagccacg	tttgccac	aaagttcg	gttacaac	atttattc	gagaaaac	cgactcgt	gtgagaaa	ctttccag	ccaaaccg	aaggacaa	caatattt	tcgcagtg	gaggcata	cgctacct	tagattgtcg	
agec actggtaaca ggattagcaggteg tggcctaact acggctacacaggeca ggtggttttt ttgtttgcaaggtatt ttgtttgcaaggatt ttggtcatga gattatcaaggggatt tttaaatcaa tctaaaggtatagatt tttggtcatga gattatcaaggattagatt tttggtcatgaggcac ctatctcaggggaccaca tcatcaaaggtatagggggagggggggggg	gcgaggta	agaaggac	ggtagctc	cagcagat	tctgacgc	aggatctt	tatgagta	atctgtct	gcctcgtg	gaaagtga	gaactttt	caactcag	ctctgcca	tgaaactg	tgtaatga	tctgcgat	aggttatc	ttatgcat	ctcgcatc	tegetgtt	agcgcatc	ttcccggg	atggtcgg	tcattggc	atacaatcga	atataaatca
agec actggtaace ytgg tggcctaace ycca gttaccttc rage ggtggtttt yatt ttggtcatga yatt ttggtcatga yatt tttgaatcaa yatt tttgaatcaa ragt aatcgcccaa cggg aagatgcgt yccg aatcgcccaa ttag aaaaactca acca tatttttga tagg atggcaaga tatt aatttccc tgaa tccggtgag gcca ttacgctcg gcca ttacgctcg ttct tctaatacc atca ggagtacgc atca aaccggcgc ttct tctaatacc	gattagca	cggctaca	aaaaagag	tgtttgca	ttctacgg	attatcaa	ctaaagta	tatctcag	gctgaggt	catccagc	tggtgatt	tctgatcc	cagcgtaa	gagcatca	aagccgtt	ctggtatc	gtcaaaaa	tggcaaaa	atcaaaat	aaatacgc	gaacactg	gaatgctg	aaaatgct	atctgtaa	tcc	atttataccc
dago con control cont	ctggtaac	ggcctaac	ttaccttc	gtggttt	ctttgatc	tggtcatg	ttaaatca	gtgaggca	gggggggg	atcgcccc	gtggacca	agatgcgt	cccgtcaa	aaaactc	atttttg	tggcaag	atttccc	ccggtgag	tacgctcg	gagcgaga	accggcgc	ctaatacc	gagtacgg	tgaccatc	tggc	tcgcgagccc
oragination of the control of the co	gcagcagc	ttqaaqtg	ctqaagcc	gctggtag	caagaaga	taagggat	aaatgaag	tgcttaat	tgactccg	ccaggcct	ttigttgt	gttgtcgg	aagccgcc	tctgatta	tcaatacc	ttccatag	caacctat	acgactga	ggccagcc	gattgcgc	atcgaatg	ggatattc	gcatcatc	cagtttag	aaaca	cccgacatta

12360 12420 12474 ttgtattact gtgcaatgta tgat ataacaccc tttttatctt ccccgagct tgatgatata tracacaca aatatggctc ttcccgttg ttattgttca caacgtggct gcagacagtt gagcaagacg ttttgagaca tegeggeete gtttatgtaa acatcagaga

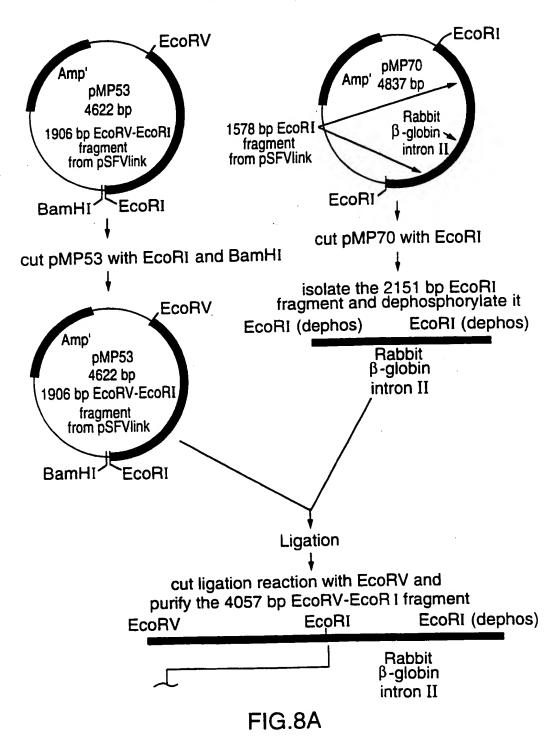
BamHI site for insertion of heterologous inserts 8677 9544 Hepatitis Delta virus ribozyme (antigenomic) - 9543 - 3678 Rabbit (-globin intron II 3679 -(before intron) 684 SFV replicon (after intron) 4252 Kanamycin Gene 12342 - 11503 682 SFV replicon CMV promoter

27/39 Subcloning of the SFV replicon



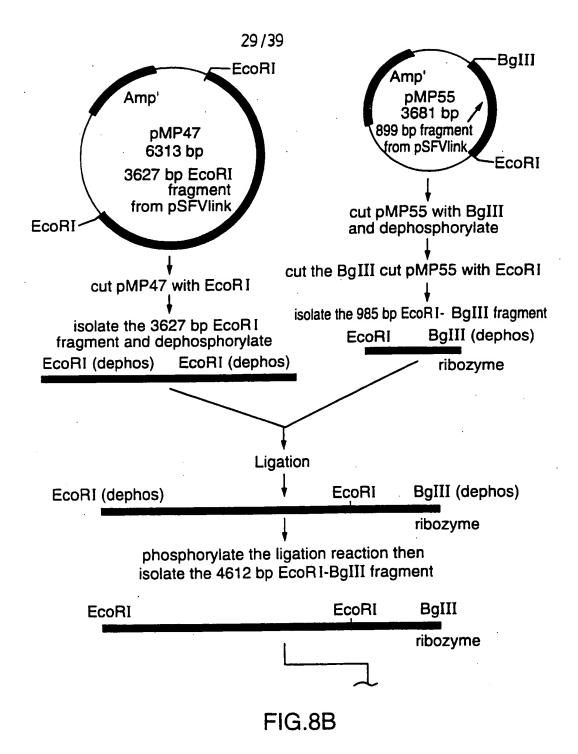
WO 99/25859 PCT/CA98/01065

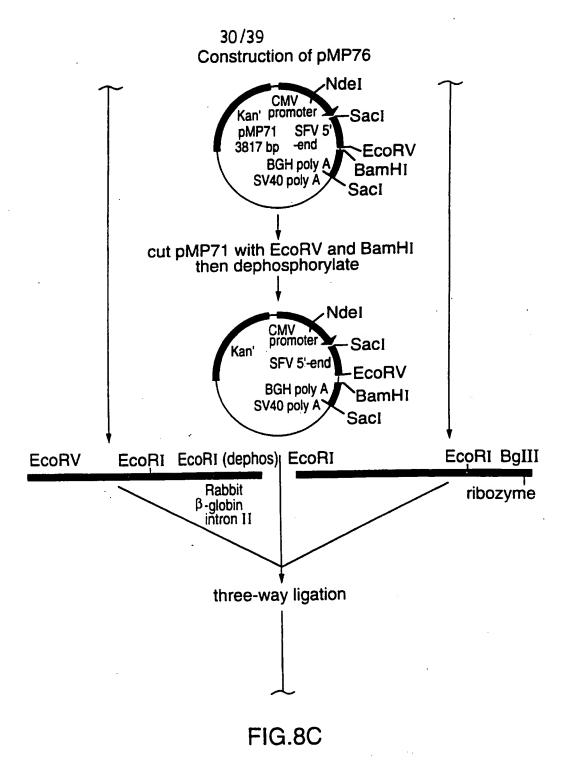
28/39 Construction of pMP76



SUBSTITUTE SHEET (RULE 26)

WO 99/25859 PCT/CA98/01065





SUBSTITUTE SHEET (RULE 25)

31/39

Construction of pMP76 (cont'd)

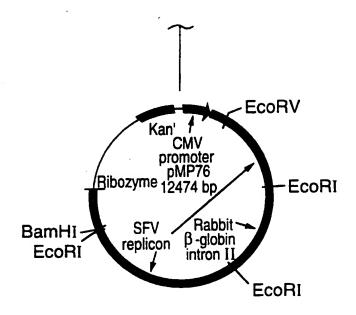


FIG.8D

32/39

Construction of pMP53 & pMP54

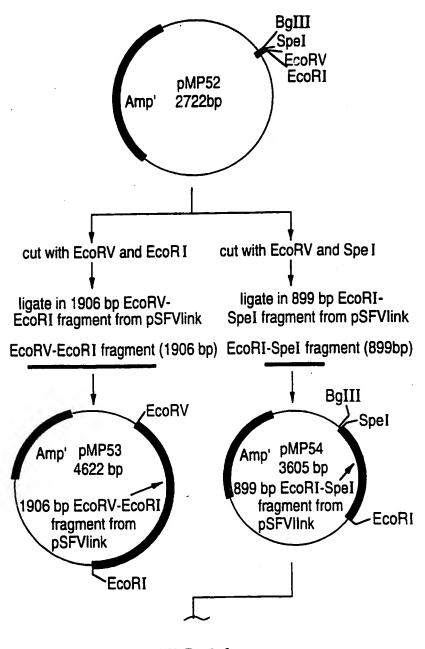


FIG.9A

33/39

Construction of pMP55

cut pMP54 with Spe I and make blunt-ended with Mung Bean nuclease

cut with BgIII and dephosphorylate

ligate in phosphorylated linker-Hepatitis Delta virus ribozyme (antigenomic)

 $\label{local_condition} \begin{center} \textbf{CGGGTCGGCATGGCATCTCCACCTCGCGGTCCGACCTGGGCA} \\ \textbf{CCCAGCCGTACCGTAGAGGTGGAGGAGCGCCAGGCTGGACCCGT}... \\ \end{center}$

- ...TCCGAAGGAGGACGCACGTCCACTCGGATGGCTAAGGGAGA
- ... AGGCTTCCTCCTGCGTGCAGGTGAGCCTACCGATTCCCTCTAG

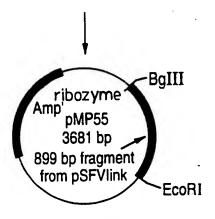
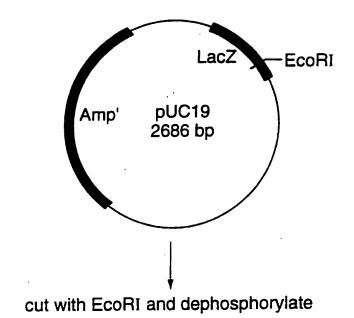


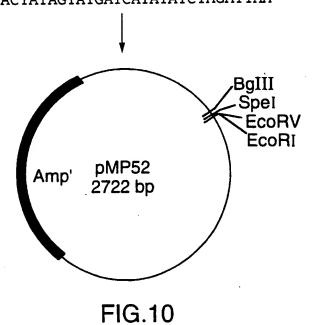
FIG.9B

34/39 Construction of pMP52



ligate in phosphorylated linker

AATTCATGATATCATACTAGTATATAGATCT GTACTATAGTATGATCATATATCTAGATTAA



SUBSTITUTE SHEET (RULE 25)

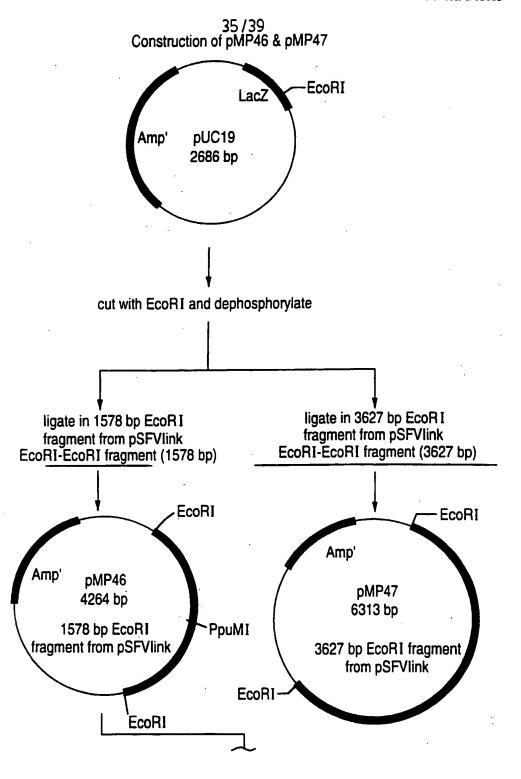


FIG.11A

SUBSTITUTE SHEET (RULE 25)

36/39

Construction of pMP70

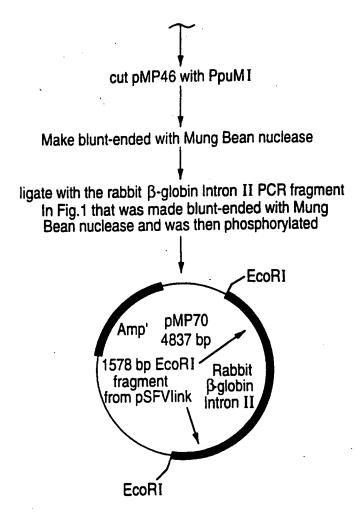
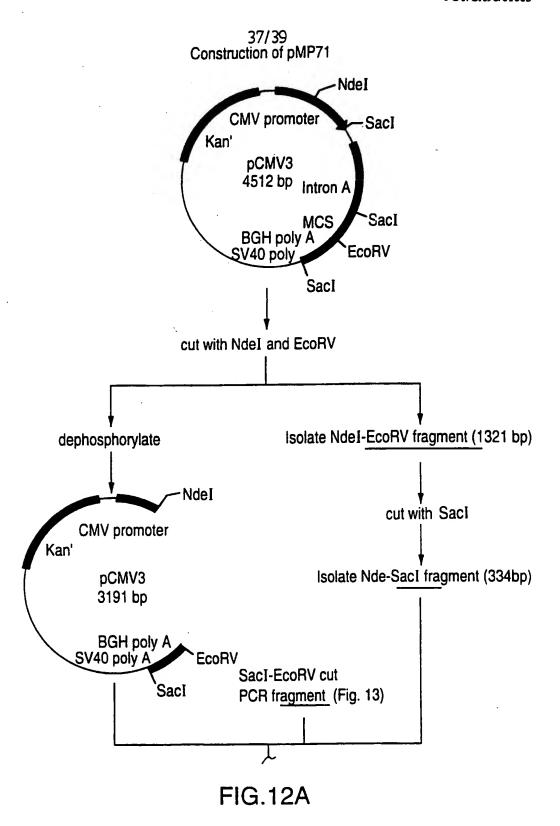


FIG.11B



SUBSTITUTE SHEET (RULE 26)

38/39

Construction of pMP71 (cont'd)

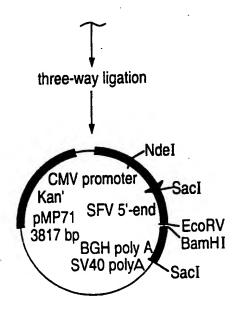


FIG.12B

292	AT	CTCATCTTGG	CAAAGACACA	AGGAGACTGA	251 TTGATCGAGC AGGAGACTGA CAAAGACACA CTCATCTTGG AT	251
250	GGCTACCAAA	TTTCGCACCT	GCCAGAGCAT	CCATGCAAAT	201 CACCAAATGA CCATGCAAAT GCCAGAGCAT TTTCGCACCT GGCTACCAAA 250	201
200	TTGCAGGTCA	GGTGGAGTCA	CGTCGTTCGA	AAGGCATTTC	151 GTCTTTGCAG AAGGCATTTC CGTCGTTCGA GGTGGAGTCA TTGCAGGTCA 200	151
150	CATTCATCAA	GCTGACAGCC	TGATATTGAG	AAGTGCATGT	101 ATGGCCGCCA AAGTGCATGT TGATATTGAG GCTGACAGCC CATTCATCAA 150	101
100	ACCACCCACG	CGAGAGATTA	CTCCGCTACG	TTTGTTCCAG CTCCTGCCAC CTCCGCTACG CGAGAGATTA ACCACCCACG 100	TTTGTTCCAG	51
00	GCCAAAAGAT	CATACACGAC	GGATGTGTGA	CGTTTAGTGA ACCGTATGGC GGATGTGTGA CATACACGAC GCCAAAAGAI 30	CGTTTAGTGA	⊣

39/39

INTERNATIONAL SEARCH REPORT

Inten anal Application No PCT/CA 98/01065

		J	1 C17 CH 30/ 01003
A. CLASS IPC 6	SIFICATION OF SUBJECT MATTER C12N15/86		
According	to international Patent Classification (IPC) or to both national classifi	ication and IPC	
	SEARCHED		
Minimum di IPC 6	ocumentation searched (classification system followed by classifica C12N	tion symbole)	
Documenta	ttion searched other than minimum documentation to the extent that	such documents are includ	ed in the fields searched
Electronic o	data base consulted during the international search (name of data be	ase and, where practical s	earch terms used)
ł			
	•		
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the re	levant passages	Relevant to claim No.
Y	WO 95 27044 A (BIOPTION AB ;LILJ	ESTROEM	1-14
	PETER (SE); GAROFF HENRIK (SE))		
	12 October 1995 cited in the application		
	see the whole document, especial	ly page 8.	
	lines 12-22		
Υ	WO 96 40945 A (CONNAUGHT LAB ;LI	VIAOMAO	1-14
'	(CA); EWASYSHYN MARY E (CA); SAME	SHARA SU)	1-14
	19 December 1996		İ
	cited in the application	ly name 6	1
	see the whole document, especiall lines 2-9; page 14, lines 15-21;	iy page o, and page	·
. 1	23, lines 18-23	Page	
Α	UO 96 17072 A (VIACENE INC.) 6 1	1006	1 14
<u> </u>	WO 96 17072 A (VIAGENE INC) 6 Jur see the whole document	ie 1330	1-14
	-	-/	
	ner documents are listed in the continuation of box C.	X Patent family me	mbers are listed in annex.
	legories of cited documents :		ned after the international filing date
CONSIGN	nt defining the general state of the art which is not ered to be of particular relevance		of in conflict with the application but ne principle or theory underlying the
"E" earlier d	ocument but published on or after the international ate	"X" document of particular	relevance; the claimed invention
WINGE 1	nt which may throw doubts on priority claim(s) or is cited to establish the publication date of another	involve an inventive s	i novel or cannot be considered to step when the document is taken alone
citation	or other special reason (as specified) int referring to an oral disciosure, use, exhibition or	cannot be considered	relevance; the claimed invention I to involve an inventive step when the
other n	neans		id with one or more other such docu- ition being obvious to a person skilled
later th	nt published prior to the international filing date but an the priority date claimed	"&" document member of t	the same patent family
Date of the s	ictual completion of the international search	Date of mailing of the	international search report
23	3 April 1999	03/05/199	99
Name and m	nailing address of the ISA	Authorized officer	
	Europeen Patent Office, P.B. 5818 Patentiaen 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nt,		
	Fax: (+31-70) 340-2040, Tx. 31 851 epo nt, Fax: (+31-70) 340-3016	Mandl, B	

1

INTERNATIONAL SEARCH REPORT

Inter: Jnai Application No PCT/CA 98/01065

2/0		PCT/CA 9	8/01065
Calegory *	ation) DOCUMENTS CONSIDERED T BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
	or the research was a successful and a depropriate, of the research passages		A SHOVER IN CHEST INC.
A	ZHOU X. ET AL.: "Self-replicating Semliki-Forest virus RNA as recombinant vaccine" VACCINE, vol. 12, no. 16, 1994, pages 1510-1514, XP002089524 cited in the application see the whole document		1-14
	LILJESTROEM P. ET AL.: "A NEW GENERATION OF ANIMAL CELL EXPRESSION VECTORS BASED ON THE SEMLIKI FOREST VIRUS REPLICON" BIO/TECHNOLOGY, vol. 9, December 1991, pages 1356-1361, XP000616021 cited in the application see the whole document		1-14
			
.		·	i
	•		
			·
	•		
	·		
	•		
}			·
		•	
,	•		
2272212	Continuation of second sheet (July 1992)		

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No PCT/CA 98/01065

Patent document cited in search repor	ı	Publication date		Patent family member(s)	Publication date
WO 9527044	A	12-10-1995	AU	699384 B	03-12-1998
			UA	2155795 A	23-10-1995
			CA	2184261 A	12-10-1995
			EP	0753053 A	15-01-1997
			FI	963860 A	27-09-1996
			JP	9511143 T	11-11-1997
WO 9640945	Α΄	19-12-1996	AU	695527 B	13-08-1998
•			AU	6117696 A	30-12-1996
			CA	2223610 A	19-12-1996
•			EP	0832253 A	01-04-1998
			US	5843913 A	01-12-1998
			US	. 5880104 A	09-03-1999
WO 9617072	A	06-06-1996	AU	4594996 A	19-06-1996
,			EP	0797679 A	01-10-1997
			US	5814482 A	29-09-1998
			US	5843723 A	01-12-1998
			US	5789245 A	04-08-1998